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ABSTRACT

In this annual report, we describe our synthetic chemical efforts for the preparation of new and novel tobacco flavorants and odorants and for the preparation of nicotine analogues. Emphasis is placed on relationships between odor and pharmacological properties and structure. These relationships serve as the basis for the choice of compounds which we synthesize. We have prepared a wide range of alkyl and acyl pyridines and pyrazines, including a series of 2,6-dialkylpyridines. The latter compounds will be compared subjectively with the analogous m-disubstituted benzenes, a number of which we have also prepared. We present results of three multidimensional scaling experiments involving alkylpyridines and pyrazines and discuss the odor dimensionalities in terms of structural features. Also discussed are odor profiling procedures.

We have completed the development of a procedure for the large scale preparation of optically pure (-)-nornicotine and (+)-nornicotine. We have synthesized 6-alkylnicotinoids by two procedures, one involving alkyllithium reagents and the other using alkyl radicals; the latter results in products which we believe are optically pure. We have also prepared a series of hydroxynicotinoids and have converted one of them to 6-chloromethylnicotine. A number of additional analogues were prepared. These compounds are being examined in a variety of behavorial and pharmacological tests and are also being used to isolate CNS nicotinic receptors.

I. INTRODUCTION

This report summarizes the accomplishments of Charge No. 2500 personnel listed below:

J. I. Seeman (Project Leader)

C. G. Chavdarian

L. E. Clawson (joined PM June, 1981)

H. V. Secor

R. Southwick

K. McCourt (co-op student, Georgia Tech)

M. Allgood (co-op student, Georgia Tech)

The effort in this project is divided into two seemingly distinct areas of research: tobacco flavorant technology [1-4] and nicotine and tobacco alkaloid chemistry and pharmacology.[4-7] The word "seemingly" was underscored in the sentence above because we have been utilizing the experiences and expertise obtained in each of these two fields to help solve problems in the other. There are basic, fundamental similarities in the goals of these two programs. In both cases, we are dealing with substances which can interact with living organisms eliciting some particular response(s).

With regard to tobacco flavorants, we are interested in the odor and flavor of specific tobacco constituents and related compounds. When we deal with nicotinoids, we may be interested in peripheral or central nervous system properties or perhaps the response of a particular compound on an isolated system, e.g., guinea pig ileum.

Table I summarizes some of the commonalities between the goals of the nicotine program and the goals of the flavor program. In

both cases, we must first identify and define the properties we are measuring. For the nicotine program, an indication of the types of tests is presented in Table II; for the flavor program, see Table III. A central theme to these discussions is illustrated in Scheme I: what are the relationships between structure and activity? This question relates to odor properties of a pyrazine just as well as to the possible hypotensive nature of a nicotine analogue.

Scheme I

Flavor <——————> Structure <——————> Pharmacological Properties

Table I

Commonalities between Nicotine Program and Tobacco Flavor Program

1. Definition and Quantitation of *In Vivo* Properties
2. Investigation of Mechanisms of Action
3. Design of Novel Compounds Possessing Specific Properties

Table II

Nicotine Analogue Activity

A. Classical Pharmacology
   1. LD_{50}
   2. Guinea Pig Ileum
   3. Rat Blood Pressure

B. Modern Pharmacological Tests
   1. Receptor Isolation and Characterization
   2. Receptor Binding
   3. Receptor Mapping

C. Behavorial Testing
   1. Cueing Properties
   2. Reinforcing Properties
   3. Tolerance-Cross Tolerance
   4. Develop Overall Behavorial Profile
D. Development of Structure-Activity Relationships

Table III

Tobacco Flavor Testing

A. Qualitative Tests
   1. Subjective Evaluations
   2. Flavor Profiling
   3. Pattern Recognition
B. Quantitative Tests
   1. Threshold Values
   2. Multidimensional Scaling
   3. Adaptation Studies
C. Development of Structure-Activity Relationships
D. Elucidate Odor/Flavor Mechanism

It is important to recognize the relationships among the three items in Table I. Thus, a knowledge of the mechanisms of action of specific tests will in theory better allow one to design compounds which will possess specific activity profiles. We believe that the converse holds equally well.

There exists today a general belief among those involved in medicinal and pharmaceutical research that there are definable relationships between the structure and physical properties of molecules and their activity. Table IV lists some of the structural parameters that are currently being used in the derivation of structure-activity relationships.

Table IV

Classical Structural Parameters Used in Structure-Activity Relationships

1. Molecular Weight, molecular size and dimensions
2. Lipophilicity
3. Solubility
4. Dipole Moment, Polarizability
5. Steric Factors
6. Electronic and Polar Factors
7. Stereochemistry, Conformation, Configuration
8. Molecular Connectivity
9. Basicity/acidity
10. Stability; potential biodegradation features

During the last few years at Philip Morris, we have observed an additional important correlation between structure and nicotine analogue pharmacological activity, that being the accessibility of the pyridine and pyrrolidine ring nitrogens to an external reagent. We suspected that such a correlation would exist because of the clear importance these two nitrogens have regarding activity. The absence of either nitrogen atom renders the resultant molecule inactive.

It is clear that nicotine's activities are receptor mediated; i.e., there exists a receptor, or group of receptors, which upon activation (interaction with a nicotinoid) causes a pharmacological response. We reasoned that the interaction between the receptor(s) and the nicotinoid involves contact between molecular fragments of the receptor and the nitrogen atoms. We further reasoned that we could model that interaction by examining a chemical interaction between the nicotinoids and the nitrogen atoms. This logic

developed into our concept of "chemical reaction modeling of pharmacological activity."

By extension, we have undertaken to examine this same concept in the field of tobacco flavorants, given the important role nitrogen containing compounds have played. Indeed, initial results have shown that nitrogen accessibility for pyridines and pyrazines is an important feature of their odor properties.

The overall strategy in both the nicotine and flavor programs is the accumulation of activity data which can be correlated with structural, chemical and physical parameters of the substances of interest. Structure-activity relationships will, hopefully, then result, from which can emanate the design and synthesis of yet additional compounds to meet specific needs or projections.

Clearly, the successful finalization of all of the goals in the nicotine and in the flavor programs, as stated in Section II.A. and III.A and summarized in Table I, is a major undertaking. We proceed in definite steps. As part of our research strategy, we have prepared nicotine analogues and candidate flavorants/odorants which can simultaneously be used to impact on as many specific research goals as possible. For example, we have prepared a series of hydroxysubstituted nicotinoids which have been of use not only in the generation of structure-activity information but also in our project dealing with isolation and identification of the nicotine central nervous system receptor(s).

To some extent, we are in the process of data collection for both programs. We have ongoing efforts in many areas described in Tables I-IV stressing a high degree of interaction among our efforts.

Clearly much of our work is collaborative and we acknowledge in Table V those individuals and groups whose contributions make possible the interdiscipilinary approach required.

Table V

Multidisciplinary Aspects of Our Programs

1. Nicotine Behavorial Testing Program: Charge #1600: Victor DeNoble, Paul Mele, Yvonne Dragan.
2. External Testing Program: T. S. Osdene, Prof. Leo Abood, University of Rochester; Bob Pages, Jim Charles.
3. Tobacco Flavorant Subjective Analyses: SEF; Dan Ennis, Archie Williams, and panels members .
4. Analytical Studies: NMR group; Ronald Bassfield, Richard Cox, and Jan Wooten.
5. Computer Applications: James Kao, Victor Day.

In this report, we will focus primarily on the chemical aspects of our work. We will, for the first time, also discuss some of our tobacco flavor subjective studies from a structure-odor relationship point of view.

II. FLAVOR CHEMISTRY[1-4]

A. Objectives

1. To evaluate a broad base of tobacco flavor types.
2. To develop novel flavor systems.
3. To develop structure-activity relationships in flavor systems which have importance in the tobacco field.

4. To develop and maintain an expertise in areas known to be important to tobacco flavor.
5. To assist Flavor Development.
6. To follow-up flavor leads developed by other PM areas.
7. To initiate work which could have impact with respect to flavors and commercial products.
8. To develop an understanding of how flavorants can contribute to low tar systems.
9. To develop methods for the non-semantic evaluation of flavorants.
10. To develop a patent position in tobacco flavorants.
11. To understand the mechanisms of the flavor response, expecially as related to tobacco flavorants.

B. Overview of Flavor Research

To some extent, we have used the terms odorant and flavorant interchangeably. One major goal of our work is to develop an appreciation of how the chemical structure of an odorant affects its perceived odor, and by implication, its flavor. Odor properties, rather than flavor, are being studied because the experimental protocol is simpler. Furthermore, a flavorist is guided in choice of flavorants in large part by the odor of the material. Although odor studies are seemingly simpler, nonetheless, they are still extremely complex, involving ultimately a subjective evaluation.

In order to discuss our results pertaining to the above objectives, we can classify our efforts into a number of discrete but

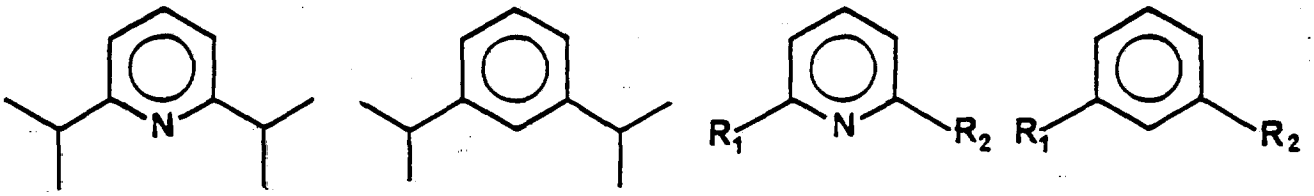
highly interactive areas. These are: (1) synthesis of potential flavorants/odorants; (2) development and on-going utilization of advanced methods of subjective analyses; (3) participation in an international program aimed at the characterization of environmental odors, and (4) isolation and identification of potentially interesting flavorants/odorants.

C. Synthesis of Flavorants

1. Most of our efforts during the past year in this area have been directed toward the synthesis of alkyl and acyl pyridines and pyrazines. These types of compounds hold significant interest in the tobacco flavor area as judged by previous experiences here in R&D as well as numerous patents and publications from other laboratories. We have three general uses for the compounds we have prepared: (1) subjective evaluation for tobacco product utilization; (2) participation in our structure-odor studies; and (3) increasing our patent coverage.

2. Alkylpyridines are well-known tobacco flavorants. A few months ago, we noted[4] that the odor of 2,6-diisopropylpyridine (1) was very similar to that of m-diisopropylbenzene (2). In contrast, it is well known that pyridine and benzene have quite different odors. Based on our structure-activity studies in the nicotine field, we tentatively concluded that nitrogen accessibility was an important factor in pyridine and pyrazine odor characteristics. To test this hypothesis, we[1] have been preparing a series of 2,6-dialkylpyridines, 3, and m-dialkylbenzenes, 4, where the substituents can be the same or different.

Pending a few purifications, we have completed the synthesis of this series of compounds (See Scheme II).



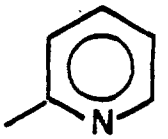
1 2 3 4

R_1, R_2=Me,Et,i-Pr,t-Bu,etc.

We[1] are now in the process of synthesizing the m-disubstituted benzene, 4, which are analogous to the 2,6-dialkyl-pyridines 3.

Scheme II. Preparation of 2,6-Dialkylpyridines.

R_6=Methyl, R_2=alkyl



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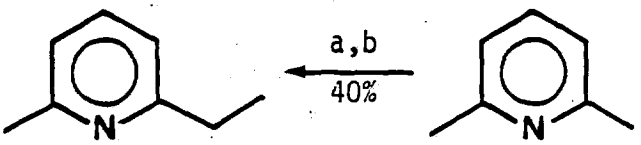
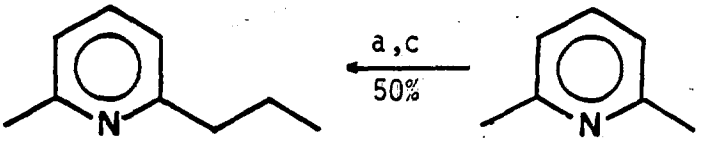
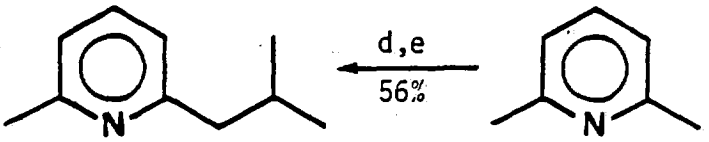
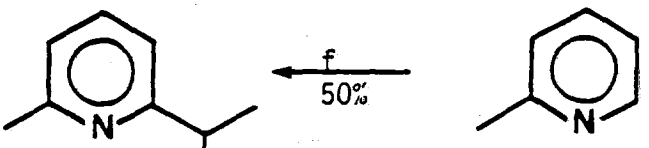
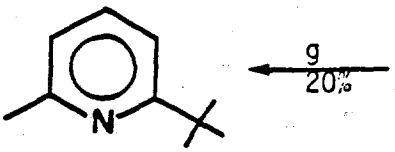




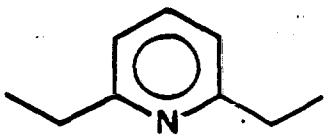






$(CH_3)_3CONHCH(CH_3)_2$+ $CH_3C(O)NHPh$

R_6=ethyl, R_2=alkyl



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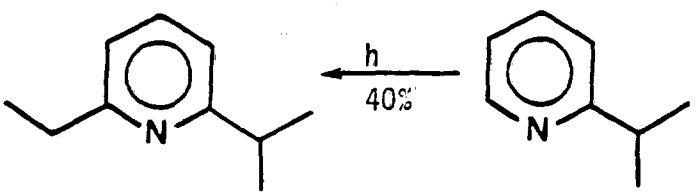
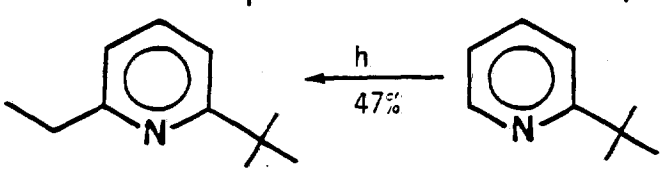
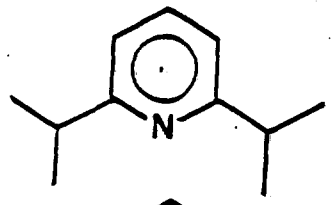




R_6=isopropyl, R_2=alkyl



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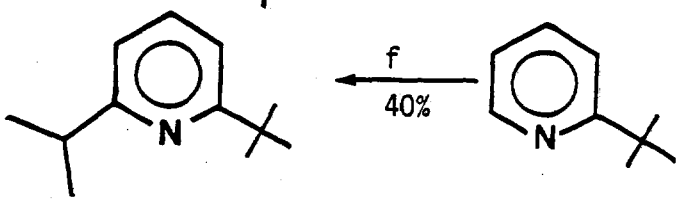
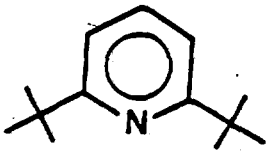


R_2=R_6=t-Bu



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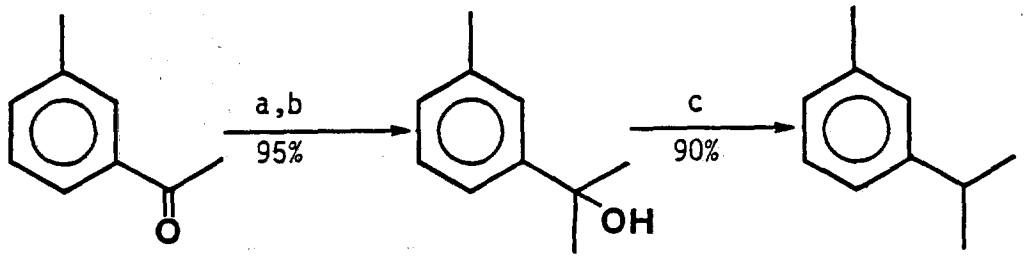
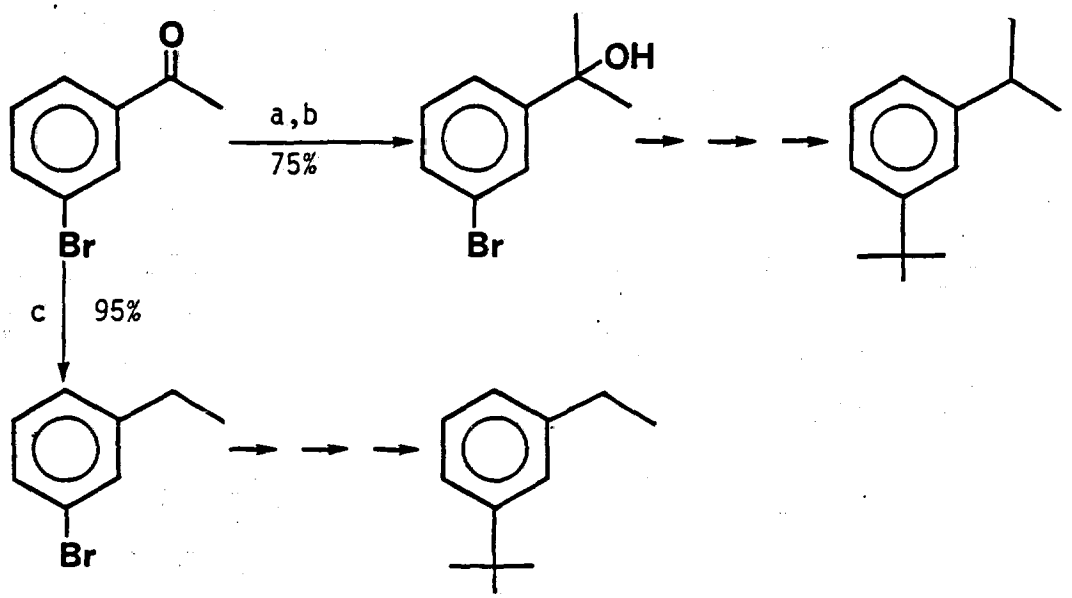
(a) lithium diisopropylamide/THF, (b) methyl iodide, (c) ethyl iodide, (d) phenyllithium, (e) isopropyl bromide, (f) isopropyllithium, (g) heat, (h) ethyllithium.

The synthesis of these types of compounds is quite difficult because they are meta substituted. Eq. 1-2 exemplify our work and indicate the type of synthetic effort which will complete the series.

(1)

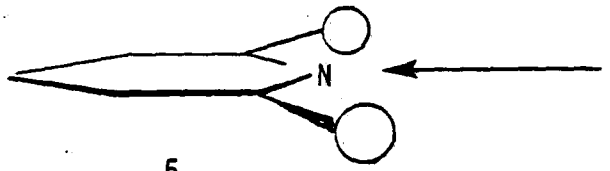


(2)



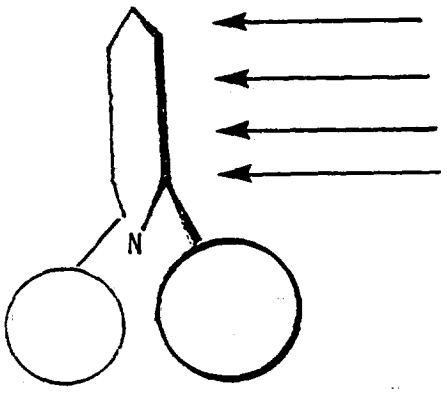
(a) MeMgBr, (b) H^+, (c) $H_2/Pd/C$.

Even though the formal subjective analyses have not yet begun, we are very excited about the comparison between the series 3 and 4 because we anticipate being able to distinguish between modes of molecule-receptor interactions; e.g., see 5 and 6. This is because benzene and its alkyl substituted derivatives have no nitrogen, and any interaction is likely to be along the face of the molecule rather than toward its edge. For compounds in which R is small (e.g., methyl) there should be a clearly perceptible difference in odor arising from head-on interactions in one case and face-to-face in the other. As R becomes larger the head-on interaction will become unfavorable and in both cases the interaction will be face-to-face. This will be reflected in nearly identical odor properties.



25

Head-on-head interaction when
C_2 and C_6 are small



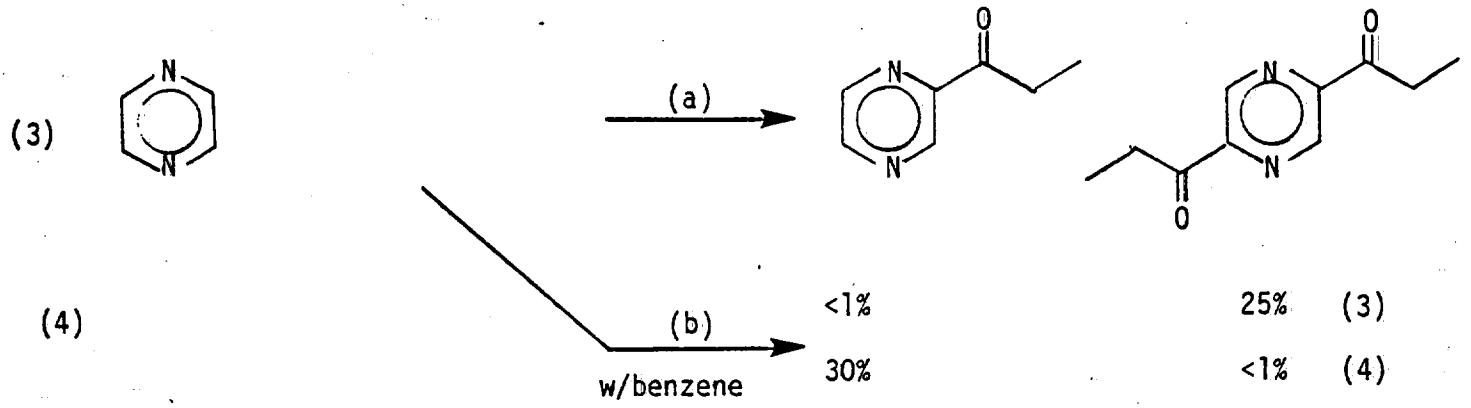
26

Face-to-face interaction when
C_2 and C_6 substituents are large

3. Table VI lists a series of monoacyl pyrazines prepared by free radical acylation during the past year[2] as part of a collaboration with David Williams (Charge #2520) and Yoram Houminer (Charge #2515). The eleven listed acylpyrazines have very similar structures but have vastly different flavor characteristics. We are particularly interested in those exhibiting "sweet" and "chocolate" responses.

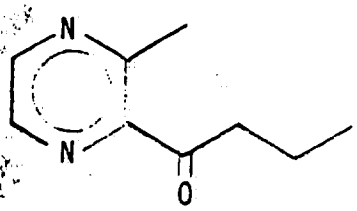
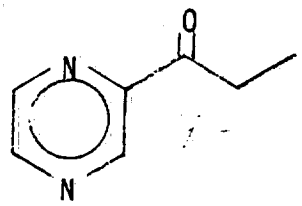
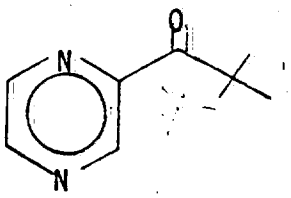
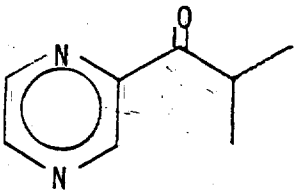
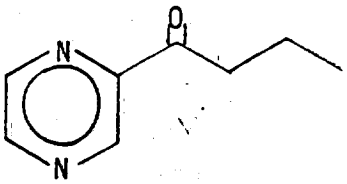
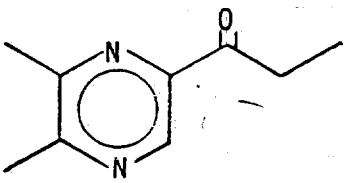
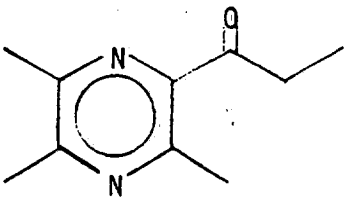
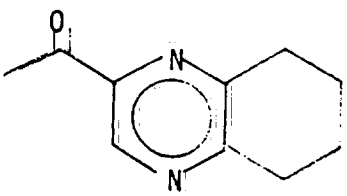
As can be seen from Table VI, the free radical acylation of N-heterocycles has developed into a fruitful area of investigation. The reaction presents some interesting aspects of chemistry and gives us the ability to prepare a vast array of novel flavoring materials.

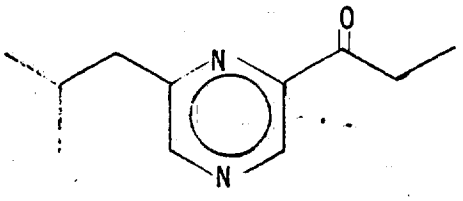
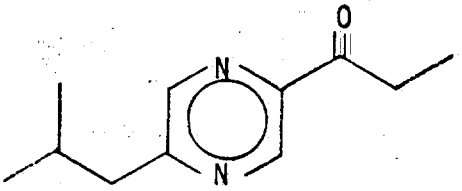
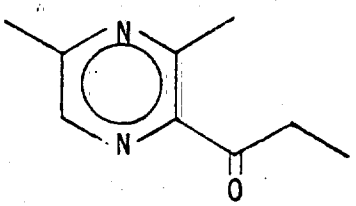
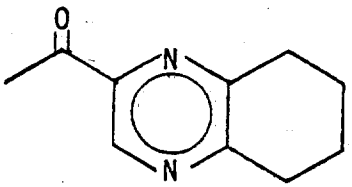
Equation 3 is a typical example of the literature preparations of acylpyrazines. The reaction of propionaldehyde with pyrazine under free radical conditions leads to almost undetectable amounts of monoacylated product 6 and low, but respectable and useful, yields of diacylated material 7. We reasoned[2] that if the monoacyl product could be removed from the reaction mixture as it forms, then the introduction of a second acyl group would not occur. Indeed, when the reaction was carried out under heterogenous conditions, monoacylation was nearly the exclusive result with only trace amounts of di-acylation. (See eq. 4.) This discovery has culminated in the filing of a process patent for the preparation of monoacyl pyrazines. The few acylpyrazines described in the patent literature generally are popcorn-nutty in character. As can be seen, the variety of structures now accessible gives a much broader range of flavor properties.



(a) Fe^{II}, t-BuO_2H, (b) Fe^{II}, t-BuO_2H, benzene

Table VI. Subjective Evaluations of Mono-acylpyrazines

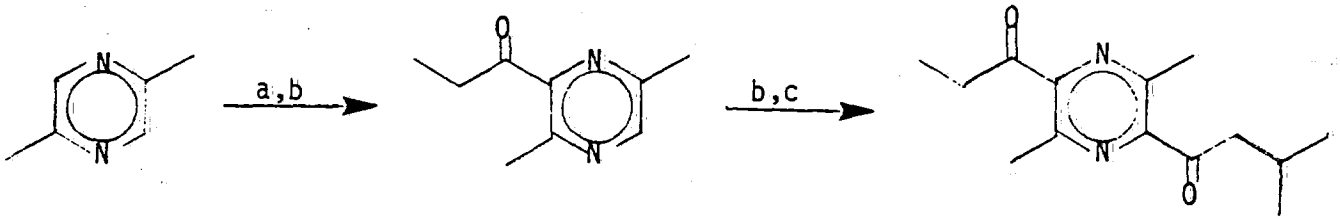
Compound	Incorporation Level	Subjective Response[b]
	10ppm	inc. response, sweeter
	86ppm	more body & smoother (rod odor)
	95ppm	like ethyl β-methylvalerate
	57ppm	NSD[a]
	94ppm	waxy, soapy
	80ppm	sweet chocolate
	91ppm	fuller, more response sl. chocolate
	111ppm	sweeter increased response

	100ppm	pleasant, woody, sweet
	74ppm	sweet chocolate
	80ppm	NSD[a]
	111ppm	sweeter, increased response

(a) no significant difference from control

(b) smoking studies

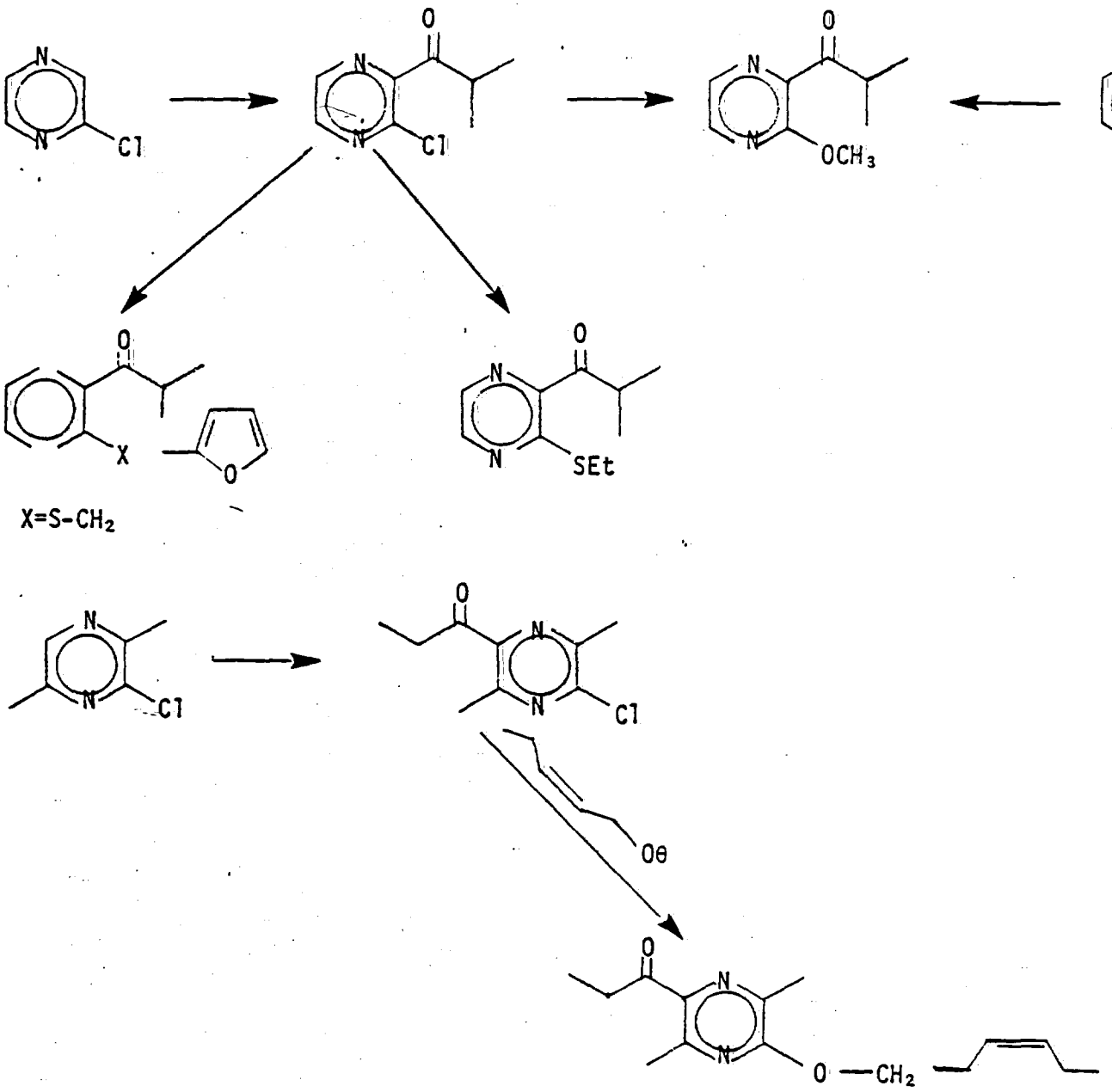
The ability to introduce one acyl group has now made possible the synthesis of diacyl pyrazines containing two different acyl groups. The feasibility of this procedure has been demonstrated by one example as shown in eq. 5. Additional examples in support of a patent application will be forthcoming.[2]

(5) 

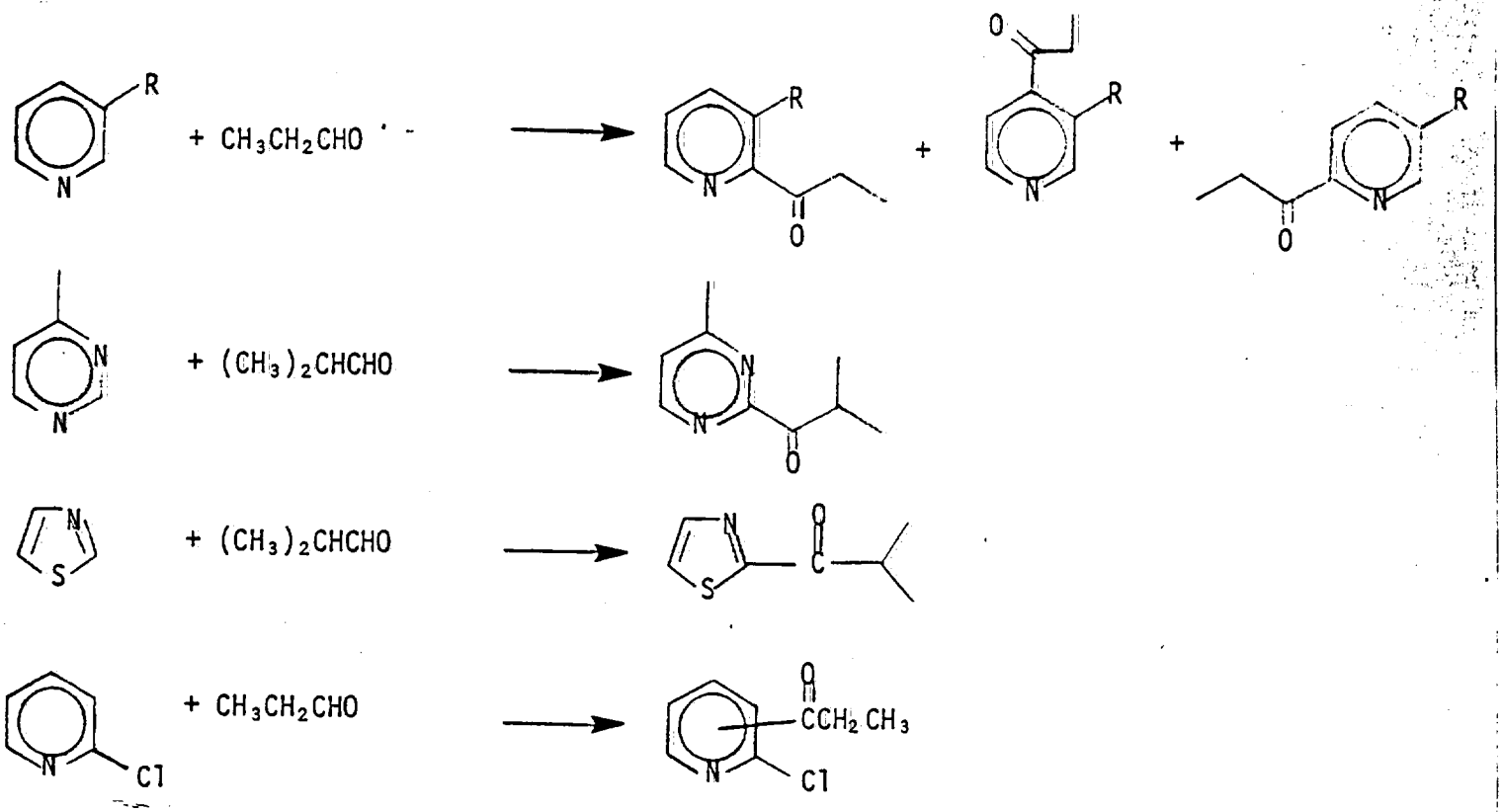
(a) CH_3CH_2CHO, (b) Fe^{II}, $\underline{t}$-BuO_2H, (c) $(CH_3)_2CHCH_2CHO$

We are also very interested in more complex heterosubstituted pyridines and pyrazines. The acylation of pyrazines bearing substituents other than carbon has been successful and a number of novel flavorants have become accessible. The reactions carried out[2] thus far are summarized in Scheme III. With the exception of simple monoacyl pyrazines, all of the above represent examples of novel compounds whose flavor properties are unknown. In addition, we are interested in applying synthetic chemical technology obtained in pyridine and pyrazine chemistry to other heterocyclic compounds which are likely candidates for tobacco flavors. In a brief excursion into the acylation of other heterocycles, the reactions shown in Scheme IV have been carried out. Complete characterization of these products is currently in progress.

Scheme III



Scheme IV



D. Subjective Evaluation of Odorants/Flavorants

1. Overview

Subjective evaluations are essential in the derivation of relationships between the sensory properties of compounds and their physical and chemical properties. Dan Ennis (Accession No. 80-177) has eloquently described the need for non-semantic sensory evaluations:

> Efforts to separate very closely related sensory properties may be rather fruitless. There is no real reason to believe that a sensory property can be adequately described by a single word in the English language. Neither the language itself nor an individual panelist's understanding of the exact meaning of words can tolerate this kind of precision. Even if words could be defined and understood exactly, there still remains the fact that complex integration of all the sensory parameters occurs at once at the moment of assessment and to expect a panelist to break down this integrated response into a series of individual semantic differential ratings is very demanding. It seems obvious from the multidimensional scaling literature on sensory dissimilarity ratings that two or, at the most, three dimensions does a very adequate job of describing the differences between gustatory or olfactory stimuli. Attempts to describe these dimensions with single words would be impossible and, in any event, unnecessary. The really important contribution is to tie the integrated dimensions to product physical and chemical properties. This should be the long-term objective of any sensory/analytical program.

Thus an essential feature in the development of odor-structure relationships is the quantification or numericalization of odor properties. If we are to correlate odor with structure, then we must statistically examine "sets of numbers", not verbal descriptors of odors. One aspect of this program has been to select methods to obtain subjective information in a form which can be manipulated mathematically.

During the past year, we have been involved in three different types of sensory programs for the evaluation of tobacco flavorants: (a) multidimensionsl scaling studies, which will be discussed in detail in Section II,D,3; (b) the American Society for Testing and Materials (ASTM) program; and (c) odor profiling using reference materials. These studies have been done in collaboration with individuals in SEF, in particular, Danny Ennis and Archie Williams.

2. Odor Profiling

Philip Morris has been participating in a study being conducted by ASTM to establish a reliable method to characterize environmental odors. The study, which involves the participation of approximately 150 panelists in 15 participating laboratories, is now in the final year of a three-year program. We anticipate that this study will provide experience with odor profiling and generate a data base for selecting and training panelists. It is planned to gather data on 160 odorants by the time the study is complete.[2]

In the ASTM study, the panelists are presented with a ballot listing 146 descriptors which can be rated from 0 to 5. See Figure I. Each odorant is impregnated on a balsa wood chip

Figure I. ASTM Odor Profiling Form

1	2	3	4	5	6	7	8	9	10	11	12
						1					
SAMPLE DESIGNATION							PANEL CODE			PANELIST	

(Col. 1–6, 8–10: letters or numbers. Col. 11–12: numbers only.)

ODOR QUALITY EVALUATION

* SMELL SAMPLE. YOU CAN RE-SMELL IT AS NEEDED FOR EVALUATION.
** GO THROUGH LIST BELOW. FOR EACH DESCRIPTOR, *ENCIRCLE* THAT SCORE NUMBER WHICH BEST CHARACTERIZES THE *DEGREE OF PRESENCE* OF THAT ODOR NOTE IN THE SAMPLE ODOR. IF ABSENT, *DO NOT ENCIRCLE ZERO.*
*** INITIAL OR SIGN, AND DATE.

Initial or Signature ..... Date .....

MEANING OF THE ODOR QUALITY SCALE:

ABSENT	SLIGHTLY		MODERATELY		EXTREMELY
0	1	2	3	4	5

Index	DESCRIPTOR	SCORE	Index	DESCRIPTOR	SCORE
001	FRAGRANT	0 1 2 3 4 5	031	OILY, FATTY	0 1 2 3 4 5
002	SWEATY	0 1 2 3 4 5	032	LIKE MOTHBALLS	0 1 2 3 4 5
003	ALMOND-LIKE	0 1 2 3 4 5	033	LIKE GASOLINE, SOLVENT	0 1 2 3 4 5
004	BURNT, SMOKY	0 1 2 3 4 5	034	COOKED VEGETABLES	0 1 2 3 4 5
005	HERBAL, GREEN, CUT GRASS	0 1 2 3 4 5	035	SWEET	0 1 2 3 4 5
006	ETHERISH, ANAESTHETIC	0 1 2 3 4 5	036	FISHY	0 1 2 3 4 5
007	SOUR, ACID, VINEGAR	0 1 2 3 4 5	037	SPICY	0 1 2 3 4 5
008	LIKE BLOOD, RAW MEAT	0 1 2 3 4 5	038	PAINT-LIKE	0 1 2 3 4 5
009	DRY, POWDERY	0 1 2 3 4 5	039	RANCID	0 1 2 3 4 5
010	LIKE AMMONIA	0 1 2 3 4 5	040	MINTY, PEPPERMINT	0 1 2 3 4 5
011	DISINFECTANT, CARBOLIC	0 1 2 3 4 5	041	SULPHIDIC	0 1 2 3 4 5
012	AROMATIC	0 1 2 3 4 5	042	FRUITY (CITRUS)	0 1 2 3 4 5
013	MEATY (COOKED, GOOD)	0 1 2 3 4 5	043	FRUITY (OTHER)	0 1 2 3 4 5
014	SICKENING	0 1 2 3 4 5	044	PUTRID, FOUL, DECAYED	0 1 2 3 4 5
015	MUSTY, EARTHY, MOLDY	0 1 2 3 4 5	045	WOODY, RESINOUS	0 1 2 3 4 5
016	SHARP, PUNGENT, ACID	0 1 2 3 4 5	046	MUSK-LIKE	0 1 2 3 4 5
017	CAMPHOR LIKE	0 1 2 3 4 5	047	SOAPY	0 1 2 3 4 5
018	LIGHT	0 1 2 3 4 5	048	GARLIC, ONION	0 1 2 3 4 5
019	HEAVY	0 1 2 3 4 5	049	ANIMAL	0 1 2 3 4 5
020	COOL, COOLING	0 1 2 3 4 5	050	VANILLA-LIKE	0 1 2 3 4 5
021	WARM	0 1 2 3 4 5	051	FECAL (LIKE MANURE)	0 1 2 3 4 5
022	METALLIC	0 1 2 3 4 5	052	FLORAL	0 1 2 3 4 5
023	PERFUMERY	0 1 2 3 4 5	053	YEASTY	0 1 2 3 4 5
024	MALTY	0 1 2 3 4 5	054	CHEESY	0 1 2 3 4 5
025	CINNAMON	0 1 2 3 4 5	055	HONEY-LIKE	0 1 2 3 4 5
026	POPCORN	0 1 2 3 4 5	056	ANISE (LICORICE)	0 1 2 3 4 5
027	INCENSE	0 1 2 3 4 5	057	TURPENTINE (PINE OIL)	0 1 2 3 4 5
028	Cantaloupe, Honey Dew MELON	0 1 2 3 4 5	058	FRESH GREEN VEGETABLES	0 1 2 3 4 5
029	TAR-LIKE	0 1 2 3 4 5	059	MEDICINAL	0 1 2 3 4 5
030	EUCALYPTUS	0 1 2 3 4 5	060	ORANGE (FRUIT)	0 1 2 3 4 5

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KEYPUNCHER: Enter Columns 1—12 as coded in at the left. Beginning with the Column 13, enter indexes (three columns) and encircled scores (one column) in a continuous fashion, but only for those lines where a score is encircled. If continuation cards needed, repeat Columns 1—12 on each card.

Index	DESCRIPTOR	SCORE	Index	DESCRIPTOR	SCORE
061	BUTTERY (FRESH)	0 1 2 3 4 5	104	HOUSEHOLD GAS	0 1 2 3 4 5
062	LIKE BURNT PAPER	0 1 2 3 4 5	105	PEANUT BUTTER	0 1 2 3 4 5
063	COLOGNE	0 1 2 3 4 5	106	VIOLETS	0 1 2 3 4 5
064	CARAWAY	0 1 2 3 4 5	107	TEA-LEAVES-LIKE	0 1 2 3 4 5
065	BARK-LIKE, BIRCH BARK	0 1 2 3 4 5	108	STRAWBERRY-LIKE	0 1 2 3 4 5
066	ROSE-LIKE	0 1 2 3 4 5	109	STALE	0 1 2 3 4 5
067	CELERY	0 1 2 3 4 5	110	CORK-LIKE	0 1 2 3 4 5
068	BURNT CANDLE	0 1 2 3 4 5	111	LAVENDER	0 1 2 3 4 5
069	MUSHROOM-LIKE	0 1 2 3 4 5	112	CAT-URINE-LIKE	0 1 2 3 4 5
070	WET WOOL, WET DOG	0 1 2 3 4 5	113	PINEAPPLE (FRUIT)	0 1 2 3 4 5
071	CHALKY	0 1 2 3 4 5	114	FRESH TOBACCO SMOKE	0 1 2 3 4 5
072	LEATHER-LIKE	0 1 2 3 4 5	115	NUTTY (WALNUT, ETC.)	0 1 2 3 4 5
073	PEAR (FRUIT)	0 1 2 3 4 5	116	FRIED CHICKEN	0 1 2 3 4 5
074	STALE TOBACCO SMOKE	0 1 2 3 4 5	117	WET PAPER-LIKE	0 1 2 3 4 5
075	RAW CUCUMBER-LIKE	0 1 2 3 4 5	118	COFFEE-LIKE	0 1 2 3 4 5
076	RAW POTATO-LIKE	0 1 2 3 4 5	119	PEACH (FRUIT)	0 1 2 3 4 5
077	MOUSE-LIKE	0 1 2 3 4 5	120	LAUREL LEAVES	0 1 2 3 4 5
078	BLACK PEPPER-LIKE	0 1 2 3 4 5	121	BURNT MILK	0 1 2 3 4 5
079	BEAN-LIKE	0 1 2 3 4 5	122	SEWER ODOR	0 1 2 3 4 5
080	BANANA-LIKE	0 1 2 3 4 5	123	SOOTY	0 1 2 3 4 5
081	BURNT RUBBER-LIKE	0 1 2 3 4 5	124	CRUSHED WEEDS	0 1 2 3 4 5
082	GERANIUM LEAVES	0 1 2 3 4 5	125	RUBBERY (NEW RUBBER)	0 1 2 3 4 5
083	URINE-LIKE	0 1 2 3 4 5	126	BAKERY (FRESH BREAD)	0 1 2 3 4 5
084	BEERY (BEER-LIKE)	0 1 2 3 4 5	127	OAK WOOD, COGNAC-LIKE	0 1 2 3 4 5
085	CEDARWOOD-LIKE	0 1 2 3 4 5	128	GRAPEFRUIT	0 1 2 3 4 5
086	COCONUT-LIKE	0 1 2 3 4 5	129	GRAPE-JUICE-LIKE	0 1 2 3 4 5
087	ROPE-LIKE	0 1 2 3 4 5	130	EGGY (FRESH EGGS)	0 1 2 3 4 5
088	SEMINAL, SPERM-LIKE	0 1 2 3 4 5	131	BITTER	0 1 2 3 4 5
089	LIKE CLEANING FLUID (Carbona)	0 1 2 3 4 5	132	CADAVEROUS, Like Dead Animal	0 1 2 3 4 5
090	CARDBOARD-LIKE	0 1 2 3 4 5	133	MAPLE (AS IN SYRUP)	0 1 2 3 4 5
091	LEMON (FRUIT)	0 1 2 3 4 5	134	SEASONING (FOR MEAT)	0 1 2 3 4 5
092	DIRTY LINEN-LIKE	0 1 2 3 4 5	135	APPLE (FRUIT)	0 1 2 3 4 5
093	KIPPERY (SMOKED FISH)	0 1 2 3 4 5	136	SOUPY	0 1 2 3 4 5
094	CARAMEL	0 1 2 3 4 5	137	GRAINY (AS GRAIN)	0 1 2 3 4 5
095	SAUERKRAUT-LIKE	0 1 2 3 4 5	138	CLOVE-LIKE	0 1 2 3 4 5
096	CRUSHED GRASS	0 1 2 3 4 5	139	RAISINS	0 1 2 3 4 5
097	CHOCOLATE	0 1 2 3 4 5	140	HAY	0 1 2 3 4 5
098	MOLASSES	0 1 2 3 4 5	141	KEROSENE	0 1 2 3 4 5
099	ALCOHOL-LIKE	0 1 2 3 4 5	142	NAIL POLISH REMOVER	0 1 2 3 4 5
100	DILL-LIKE	0 1 2 3 4 5	143	FERMENTED (Rotten) FRUIT	0 1 2 3 4 5
101	CHEMICAL	0 1 2 3 4 5	144	CHERRY (BERRY)	0 1 2 3 4 5
102	CREOSOTE	0 1 2 3 4 5	145	VARNISH	0 1 2 3 4 5
103	GREEN PEPPER	0 1 2 3 4 5	146	SOUR MILK	0 1 2 3 4 5

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which is attached to each ballot. The panelist is instructed to sniff the odorant and then rate the intensity of each of the descriptors if it applies to the odorant. The collective results from 150 panelists than constitute an odor profile which characterizes the perceived odor notes for each sample.

At this stage in the study, it appears that reliable profiles can be generated. For example, the odorant acetophenone was evaluated on two different occasions several months apart and the profiles generated were essentially identical. Profiles for 1-hexanol and 1-heptanol were significantly different, indiating that the method is reasonably sensitive to small structural changes in the odorant. It appears that the reliability of the method depends on having a large number of panelists although it is not clear how large a number is necessary. We hope that this feature will be defined at the completion of the study.

A second approach involving odor profiling uses reference materials instead of word descriptors. This technique has the advantage that the panelist is comparing the test substance with the identical reference odors given to all the other panelists. The ASTM procedure is hinged on the assumption (or hope) that the panelists will have the same mental perceptions (or odor memories) for the verbal descriptors. Clearly, the verbal descriptor approach is significantly easier to administer and allows for a greater number of comparisons to be made; note that Figure I indicates 146 descriptors for each sample.

We were able to obtain the detailed results of a study performed at Naarden International as part of their program in the characterization of perfume chemicals. They used a set of 30 reference odorants and asked the panelist to rate each stimulus in comparison to the odor of the reference materials. In this way numerical data were generated which did not rely on verbal descriptors. The majority of our analyses of the Naarden work was performed by Danny Ennis and Pamela Bowman. Because the results of this project were reported in detail recently (Accession #81-237) by Pamela Bowman, we will not discuss it here.

Both of these profiling methods are suitable for characterizing odor types; i.e., they can group odorants with similar "perceived" odors. The data can be manipulated mathematically to indicate the degree of similarity among members of any grouping. Both methods depend heavily on selecting either the appropriate descriptors or reference odorants such that the entire spectrum of odor notes is included. Unfortunately, to date, there has been no satisfactory comparison of these three methods [including multidimensional scaling (MDS) which will be discussed in the next section]. We view this to be a serious deficit in the investigation of structure-odor relationships and envision comparative studies as a relatively high priority item.

3. Multidimensional Scaling

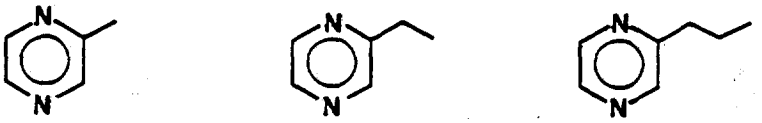
Another method which has been used successfully is multi-dimensional scaling (MDS). This is a non-semantic method of

evaluation in which the panelist is instructed to assess the degree of similarity between a pair of odorants. There is no attempt made to ascertain the basis for the judgment. By obtaining data for all pairs of stimuli, it is possible to construct a diagram showing the interrelationships among the members of the set. Unlike the profiling method, MDS does not limit the odor judgments by using reference odorants or descriptors. As a result of obtaining similarity judgments, no descriptive labels can be attached to any of the data. For the purpose of SAR studies correlating odor and chemical properties this is sufficient.

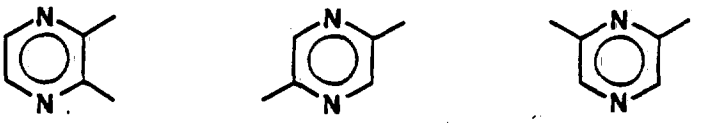
Alkyl substituted pyridines and pyrazines have been selected for these studies because they are relatively simple structures which exhibit a wide range of interesting odor notes. Two studies (MDS I and MDS II) which were carried out at Duke University formed the basis for a third study (MDS III) conducted at PM.[2] The first of these, MDS I, was designed to learn whether there was any correlation between odor and relative substituent positions or substituent size. The stimuli used are shown in Figure 2.

Figure 2. Stimuli for Multidimensional Scaling Study #I (MDS I)

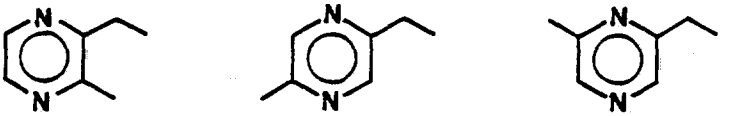
Monosubstituted:



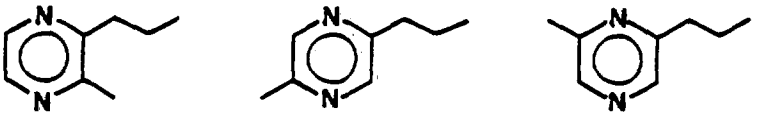
Set 1:



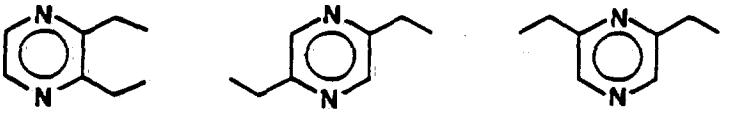
Set 2:



Set 3:



Set 4:



The structural variations included in MDS I (Figure 2) are: (a) three monosubstituted unbranched pyrazines; and (b) four sets of 2,3-, 2,5- and 2,6-disubstituted pyrazines incorporating the substitutents found in the monosubstituted series.

Figure 3a displays the three dimensional space which represents the subjective data for MDS I with the odorants shown in Figure 2. The small sphere at the top of each vertical line represents the point in space for the odorant indicated. We comment that each (x,y,z)-coordinate actually represents a region in space whose volume and shape can be generated by a complex statistical procedure. Of course, for the MDS experiment to be meaningful, the spaces must be reproducible and there must not be significant overlap of the spatial positions of the test substances due to noise in the data. For the current discussion, we will assume, based on information in hand, that the spaces are meaningful and points do not "overlap".

A number of interesting observations may be made by examination of Figure 3. (a) In all cases, the 2,6-disubstituted compound has a larger x-coordinate and a larger z-coordinate (except for the dimethyl case) than does its corresponding 2,3- and 2,5-isomer. As seen in Figure 3b, all 2,6-isomers fall along a unique line. (b) Within each set, there is an extraordinarily significant relationship (eq. 6 and correlation shown in Figure 4) between the distance between two points measured in the (x,y)-plane and the difference in their z-coordinates. These observations suggest that two

Figure 3a. Three Dimensional Space for MDS I

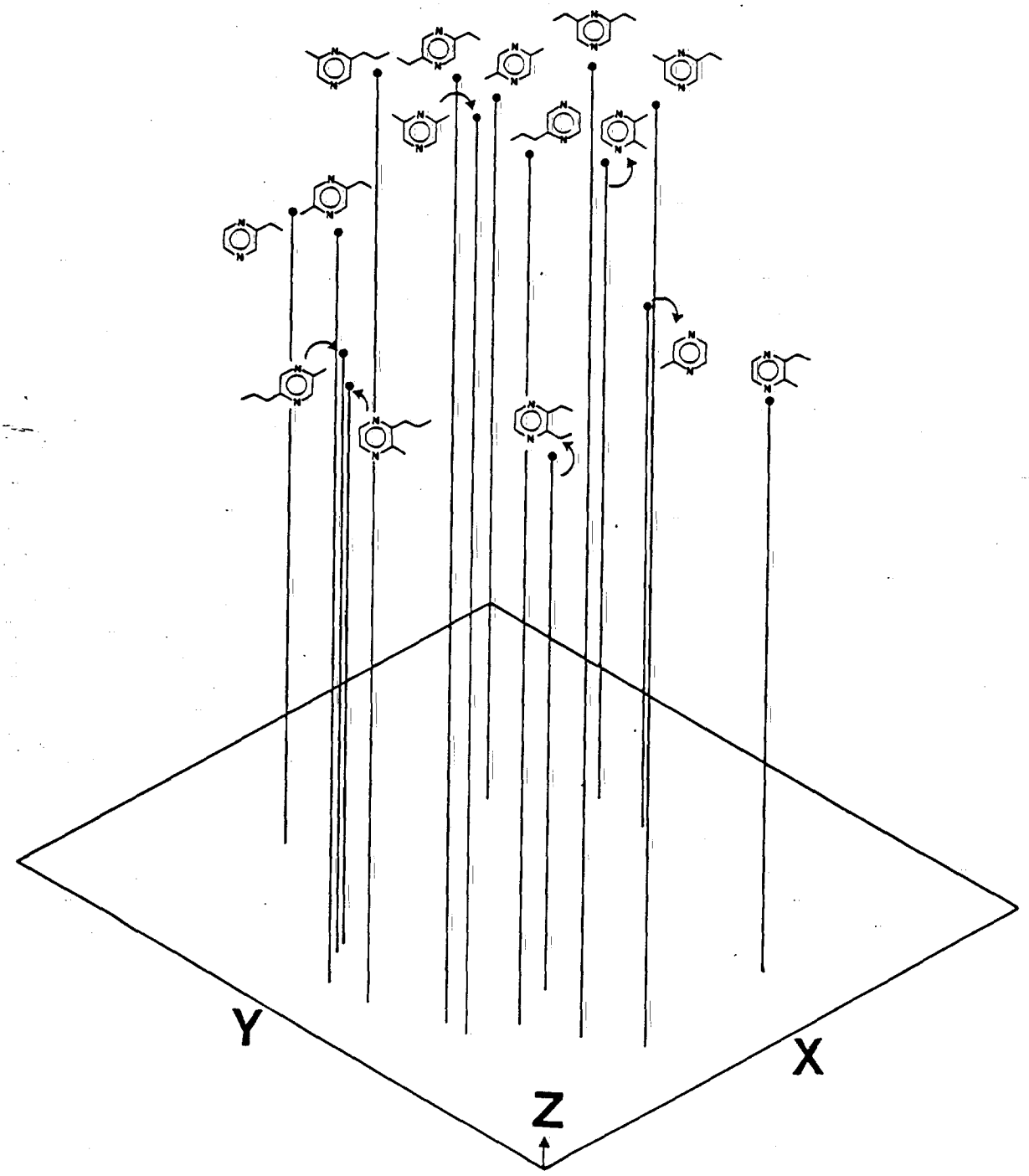


Figure 3b. Three Dimensional Space for MDS I.
x - y Projection.

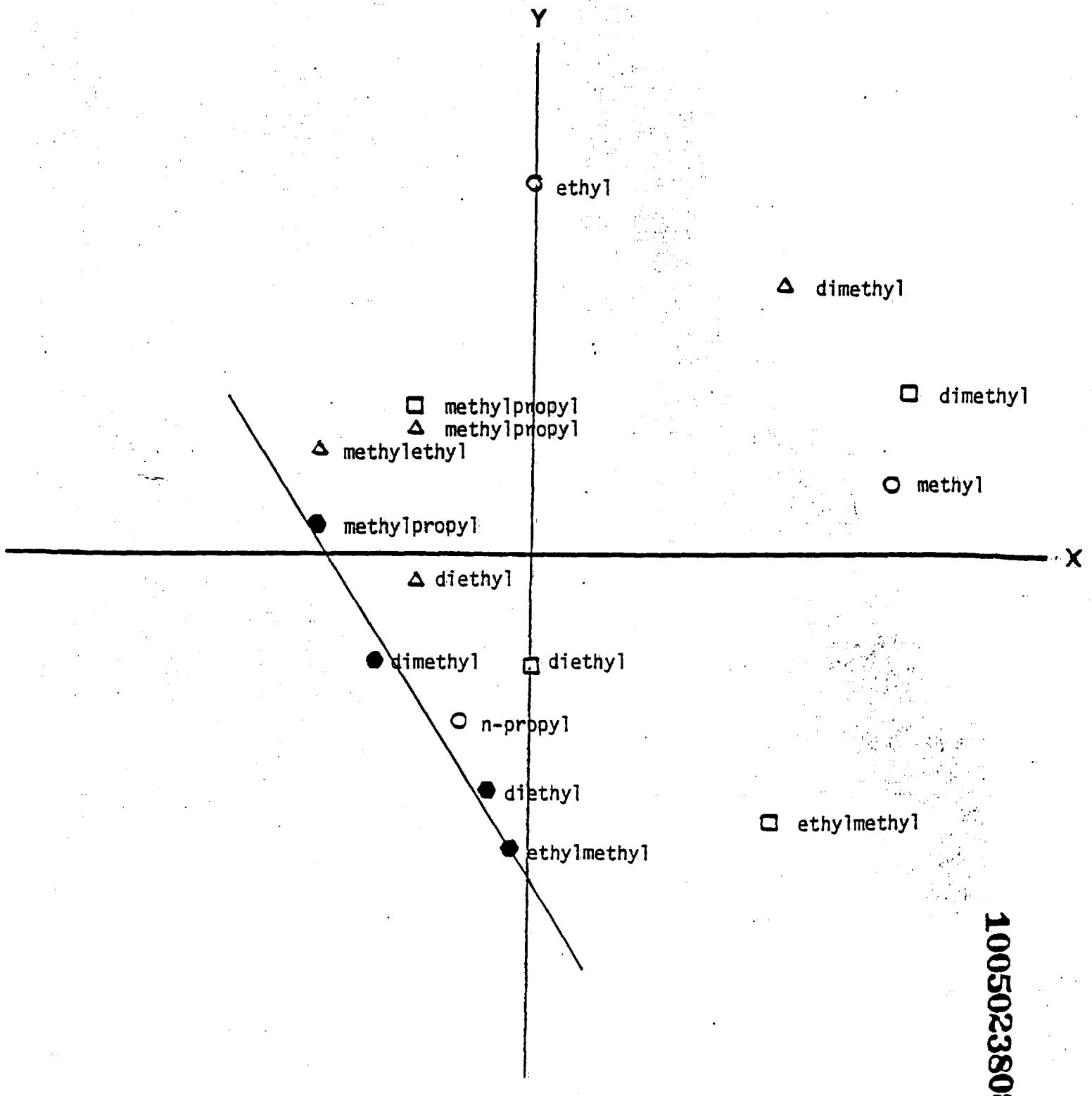


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Figure 3c. Three Dimensional Space for MDS I.
x - z Projection.

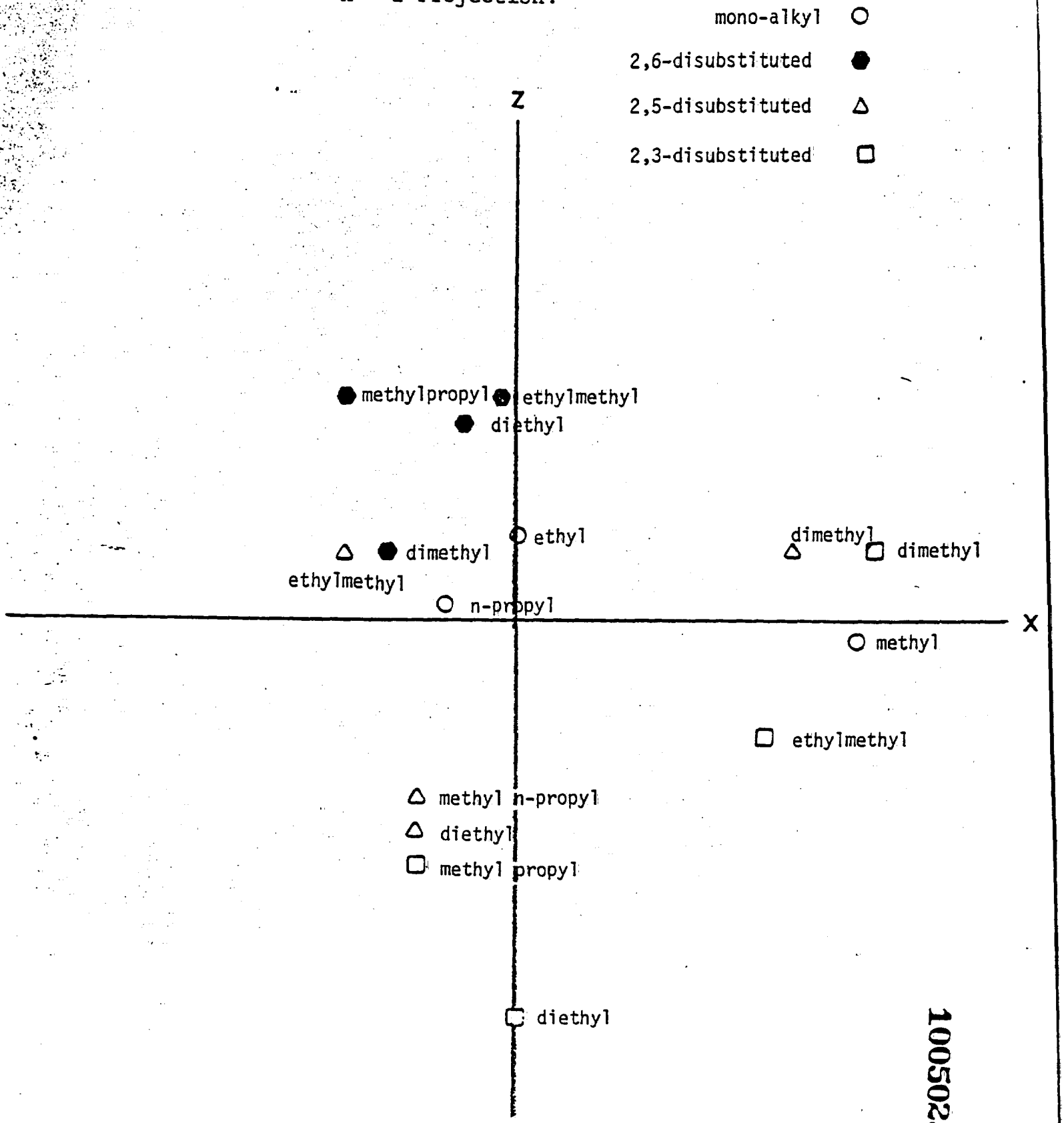

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Figure 4. Correlation for MDS I (see eq. 6)

dimensions are sufficient to "clump" the 2,6-substances from the 2,3- and 2,5-substances. (c) The monosubstituted compounds have vastly different x- and y- coordinates but very similar z-coordinates (Figure 3c). (d) There appears to be a separation which roughly corresponds to molecular weight (*c.f.* x-axis in Figure 3c). (e) In all cases, the 2,5-disubstituted entry has a more positive z-coordinate than the isomeric 2,3-substance (Figure 3c). Also, in three of the four cases (methyl-methyl, ethyl-ethyl, and methyl-ethyl), a line connecting the 2,3-point with its corresponding 2,5-point is parallel and in the same direction (Figure 3a).[2,4]

$$(6)\quad d_z = 1.3\, d_{x,y} + 142$$

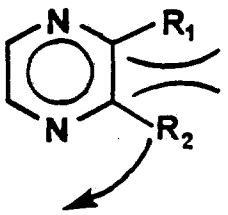
[correlation coefficient = .964, n = 8, std deviation of residuals = 13.4, probability = .00035]

where $d_z = z_{26} - z_j$, 26 referring to the 2,6-disubstituted substance and j referring to either the 2,3- or 2,5-substance, and $d_{x,y} = [(x_{26}-x_j)^2 + (y_{26}-y_j)^2]^{\frac{1}{2}}$

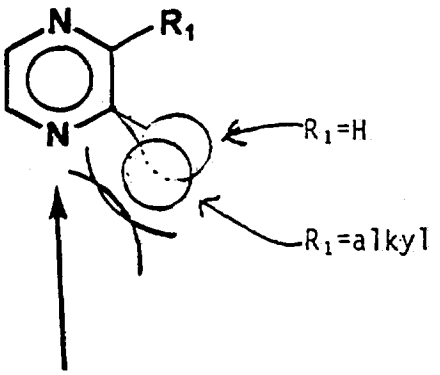
We emphasize that the above observations (a)-(e) were purely by "eye".

We are in the process of applying more sophisticated statistical procedures for the analysis of these data. Nonetheless, we are optimistic concerning the value of this type of experiment in terms of structure-odor conclusions. We thus take the structure-odor relationship "plunge" at this early stage in our work by making the following conclusions. (i) Nitrogen accessibility is an

important factor in pyrazine odor. The interaction with the appropriate receptor(s) distinguishes between one and two reasonably accessible nitrogen atoms for complexation. (ii) the importance of the molecular weight to odor may be related to the dominance of "pleasantness" in the perceptions of the panelists. Possibly, the less accessible the nitrogens, the less distasteful the odor. We shall come back to the nitrogen accessibility and molecular weight themes in MDS II and MDS III. (iii) Observation (e) above may well be related to a buttressing effect in the 2,3-system which is not present in the related 2,5-system. Buttressing is a term which indicates that the spatial proximity of two (or more) groups results in a sterically hindered situation. To diminish the destabilizing effects of buttressing, the groups spread apart as indicated in 7. One net effect of this change in position of the substituents is their "apparent" increase in size, *c.f.* 8. Buttressing effects in 2,3-disubstituted pyrazines are thus related to the accessibility of the adjacent nitrogens, as shown in 8.[2,4]



7



decreased nitrogen accessibility

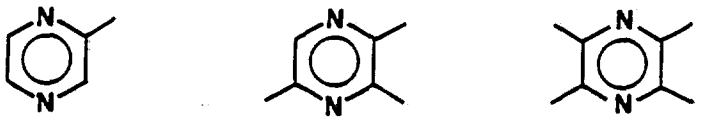
8

Our recognition of the apparent ubiquity of the nitrogen accessibility concept in the analysis of the MDS dimensions was to some extent related to our finding that nitrogen accessibility was important in the understanding of nicotine pharmacology. Interest in correlating chemical structure with nitrogen accessibility and chemical reaction modeling (rates of alkylation of substituted pyridines) coincided nicely with the indication from these MDS studies that the size and position of the substituent on the pyrazine ring determined the odor properties. The chemical literature contains numerous references to the special case of two substituents affecting some property in a non-additive manner. From alkylation studies of pyridines it has been possible to quantitate this effect, usually termed buttressing. Thus, the stimuli shown in Figure 2, indicate that the odor properties are modified by the buttressing effect. To date there has not been any convincing evidence in the literature demonstrating that the principles which can be used to interpret the reactivity of organic compounds can be applied to understanding olfaction.

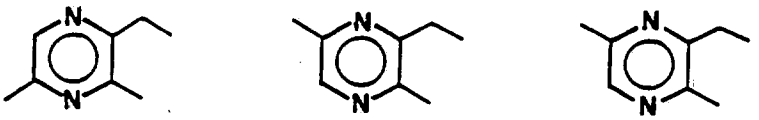
MDS II[2] involved a second set of alkylpyrazines, namely a group of dimethyl alkylpyrazines (trialkylpyrazines) in which one of the alkyl groups was systematically varied. In addition to the trisubstituted pyrazines, methylpyrazine, trimethylpyrazine and tetramethylpyrazine were included in MDS II. The stimuli are shown in Figure 5.

The three dimensional space which represents the subjective data for MDS II is shown in Figure 6. Again, there is an apparent inverse relationship between molecular weight and the z-dimension

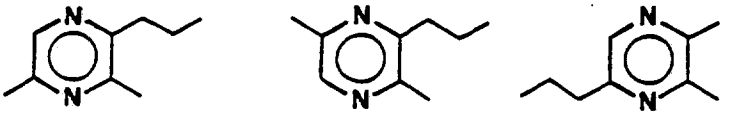
Figure 5. Stimuli for MDS II



Dimethylethyl:



Dimethylpropyl:



Dimethylbutyl:

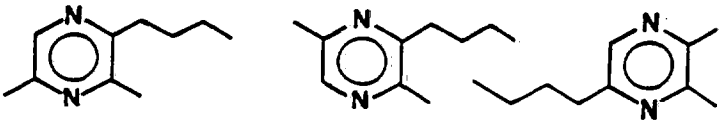


Figure 6[a]. Three Dimensional Space for MDS II

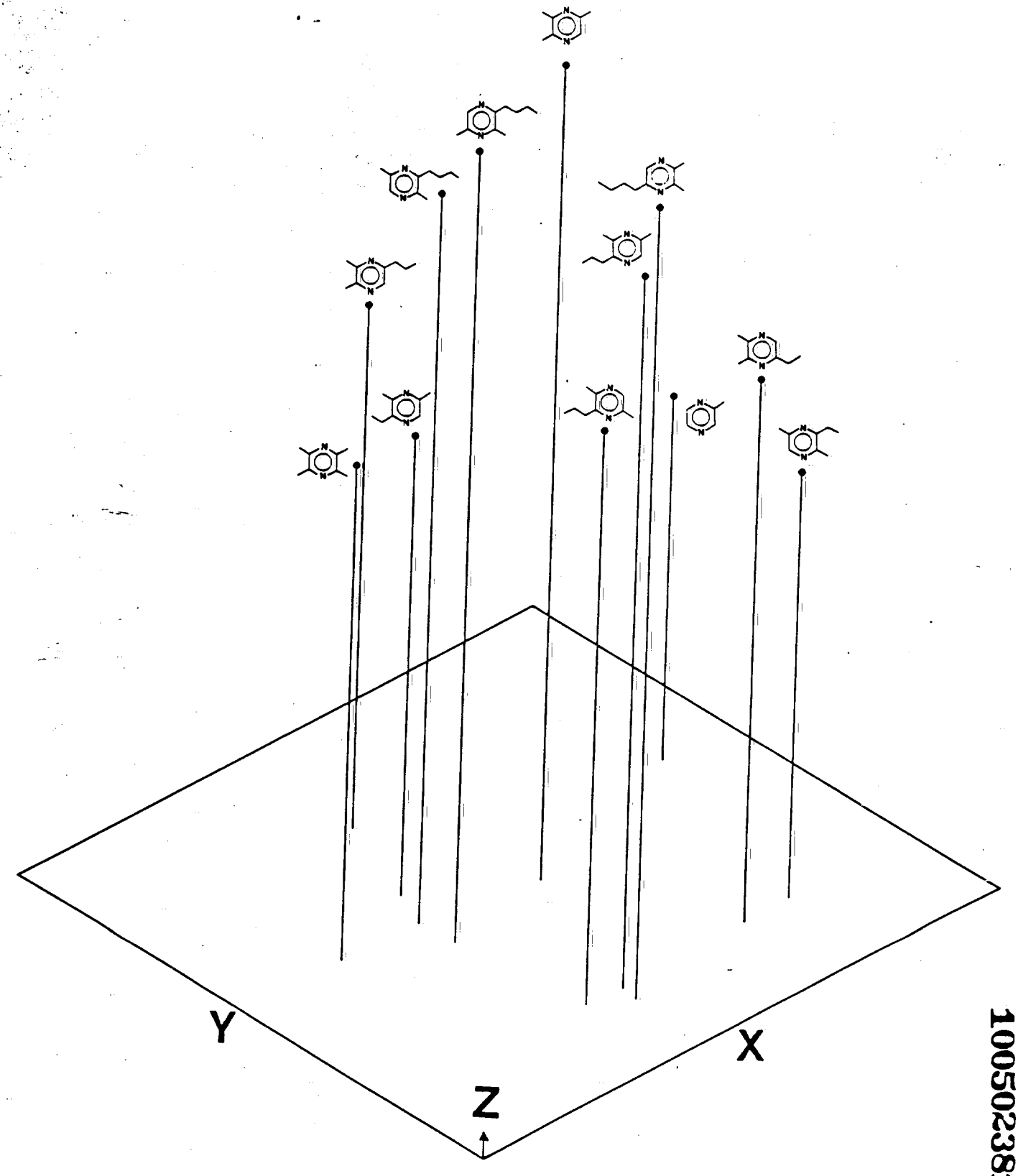
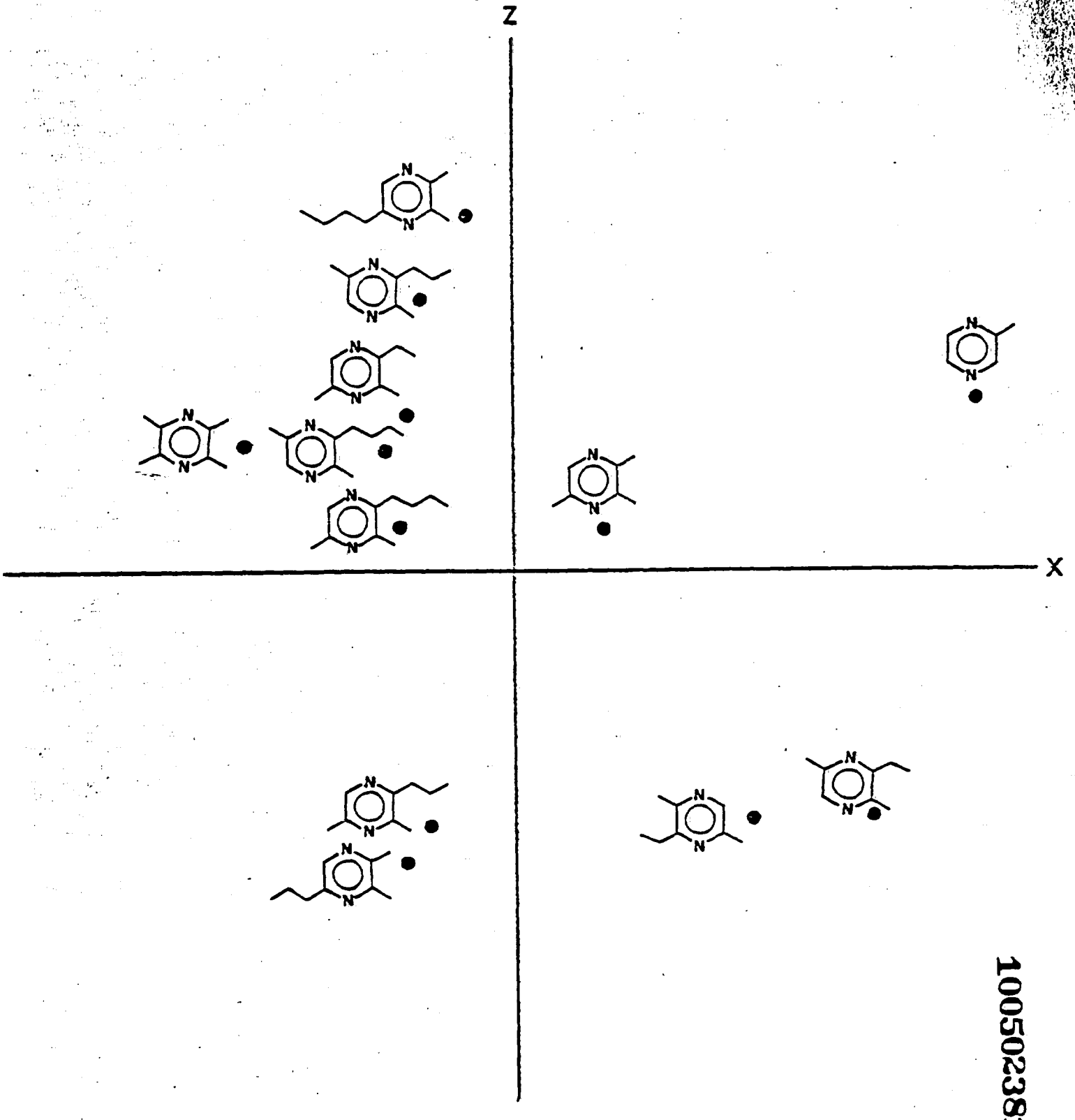


Figure 6b. Three Dimensional Space for MDS II.
x -z Projection.



(Figure 6a). In this case, there is no clear trend ascribable to nitrogen accessibility. Methylpyrazine, which is structurally quite dissimilar from the other eleven substances, is off-by-its-own, seemingly a confirmation of a structure-odor differentiation (Figure 6b). Indeed, in terms of the x-coordinate, the extremes are methylpyrazine, the molecule with the most available nitrogen atoms, to tetramethylpyrazine, the molecule with the least available nitrogen atoms (Figure 6b). The tightness of the points along the x-axis (Figure 6b) indicates that trisubstituted pyrazines are very similar, from an odor perspective. This similarity is likely due to the similarity in molecular shape and nitrogen atom congestion within this series.

As stated above, MDS I and MDS II were performed external to PM,[2] although much of the structural analyses were recently derived here by us. The compounds chosen for MDS III,[2] the subjective data for which was collected at PM, are shown in Figure 7. The compounds include a series of monosubstituted pyridines and pyrazines and a series of 2,3-dialkylpyrazines. They were chosen to reveal additional information regarding the importance of nitrogen accessibility and the nature of the pyrazine odor receptor (one or two nitrogens needed).

The compounds were either obtained from commercial sources or synthesized by unambiguous routes.[2] In all cases, the compounds were purified by preparative gas chromatography and shown to be 99% pure. Solutions were prepared by dilution in distilled water and the stimuli were presented to the panel in wide-mouth amber bottles. As a check on the procedure, one compound was presented twice so

Figure 7. Stimuli for MDS III

Pyridines

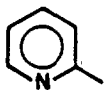
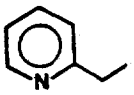
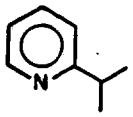
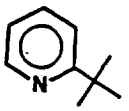
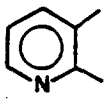
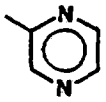
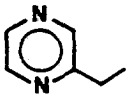
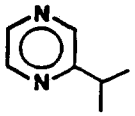
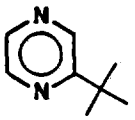
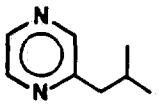
Monosubstituted Pyrazines

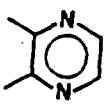
Disubstituted Pyrazines

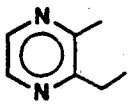
that an indication of the noise in the data could be obtained. The panelists were all R&D personnel with no special training in odor evaluations. The evaluations and data analysis were carried out largely through the efforts of Danny Ennis and Archie Williams.

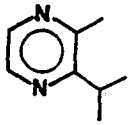
The first two panel sessions were used to familiarize the panelists with the stimuli and to adjust concentrations such that all stimuli were of the same intensity. In subsequent evaluations panelists were instructed to disregard any intensity differences and make judgments on the basis of odor quality only. During this introductory exposure to the stimuli, panelists were requested to describe each odorant in their own words. These descriptions, shown in Table VII, were used principally as a device to help focus attention on the stimuli, although there was some entertainment value for panelists to read how others had described the odor.

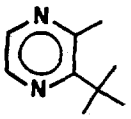
TABLE VII

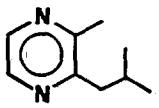
A.		oily, dirty; intense pyridine-like; pyridine; pyridine; old flounder; phenolic; light green, dusty, hospital; medicinal green
B.		oily dirty; pyridine-like; pyridine; ugh!; pyridine; dill; lawn mower grass; phenolic; medicinal; rubbery medicinal
C.		dry, mint-like, sweet; pyridine; pyridine; green; pyridine; sweet; dill pickles; sweet green dusty hospital; medicinal
D.		camphory; sweet camphor; cedar; pleasant camphory; sweet; camphor; grassy; sweet honey bug spray, green dusty toluene-like; sweet rubbery
E.		old cut green plants; pyridine; pyridine; fishy; pyridine-amine; really old flounder phenolic; dusty hospital; rubbery medicinal
F.		musty; acetone-like; pyridine sweet; slight almond; musty phenolic; toluene-like hosptial; low nutty slight green woody
G.		harsh oily green; pungent musty; slight pyridine; pyridine-popcorn; popcorn-caramel popcorn with rubbing alcohol; camphor eucalyptus; phenolic; glue; pyrazine chocolate
H.		musty oily; not pleasant; slight pyridine; green; mildly sweet; damp pungent; glue toluene-like, burnt woody; rubbery
I.		sweet oily; birch wood sauna; slight camphor; sweet spicy; sweet; sweet cherry; sweet; green dusty; green woody
J.		licorice, licorice; sweet slightly pyridine; very sweet; sweet; anisette; very sweet; sweet green floral; green sweet woody chemical

K.  dry green plants; mild woody; roasted; earthy; popcorn; caramel popcorn; popcorn; glue pungent burnt; chocolate; nutty, slight sulfurous

L.  harsh oily green; nutty aromatic; roasted; earthy; strong popcorn; popcorn; pungent musty; pyrazine sweet, light green; nutty, slight popcorn cereal

M.  green; musty penetrating; slight camphor; sweet amine; musty pungent; Vicks green medicinal; green phenolic

N.  Vicks Vaporub; smooth oily; strong vaginal smell; camphor-like; menthol; camphor; bitter camphor musty; light green medicinal sharp; woody earthy musty

O.  sweet oily; unpleasant off sweet; faint camphor-cooling; green; green weed; dill grassy; medicinal; cherry; bell pepper; weedy, slight licorice, galbazine

Data collection was completed in twelve sessions during which panelists compared all possible pairs of stimuli (10 pairs per session). Panelists were instructed to sniff each stimulus of the pair presented and then mark on a line the degree of similarity for the pair. In this way a matrix of data was obtained which, after data analysis by MDS computer programs, produced the relationships shown in Figure 8. The duplicate stimuli, isobutylpyrazine, did not exactly coincide thereby providing an indication of noise. Thus although each stimulus is represented as a point, more correctly the point is probably the focus of a region of space.

Figure 8 illustrates the three dimensional space for MDS III. A number of structural conclusions can be made.[2,4] (a) Molecular weight increases along the x-coordinate (Figure 8c). This correlation is illustrated by eq. 7 and Figure 9. (b) For pyridines and monosubstituted pyrazines, nitrogen accessibility is inversely related to the x-coordinate (Figure 8). (c) There are a number of inconsistencies relating to the isobutyl compounds. Perhaps this is a reflection of the significant conformational flexibility of an isobutyl group. (d) There is a degree of similarity in the pattern relating the 2-methyl-3-alkylpyrazines to the alkylpyridines, but these two are quite different than the monoalkylpyrazines (Figure 8a). This may again reflect the considerable nitrogen accessibility at the unhindered nitrogen in monosubstituted pyrazines.

(7) Dimension x = 0.046 MW - 5.72

[correlation coeff. = .837, n=15, probability = 0.00023, standard dev. of residual = 0.583]

Figure 8a. Three Dimensional Space for MDS III

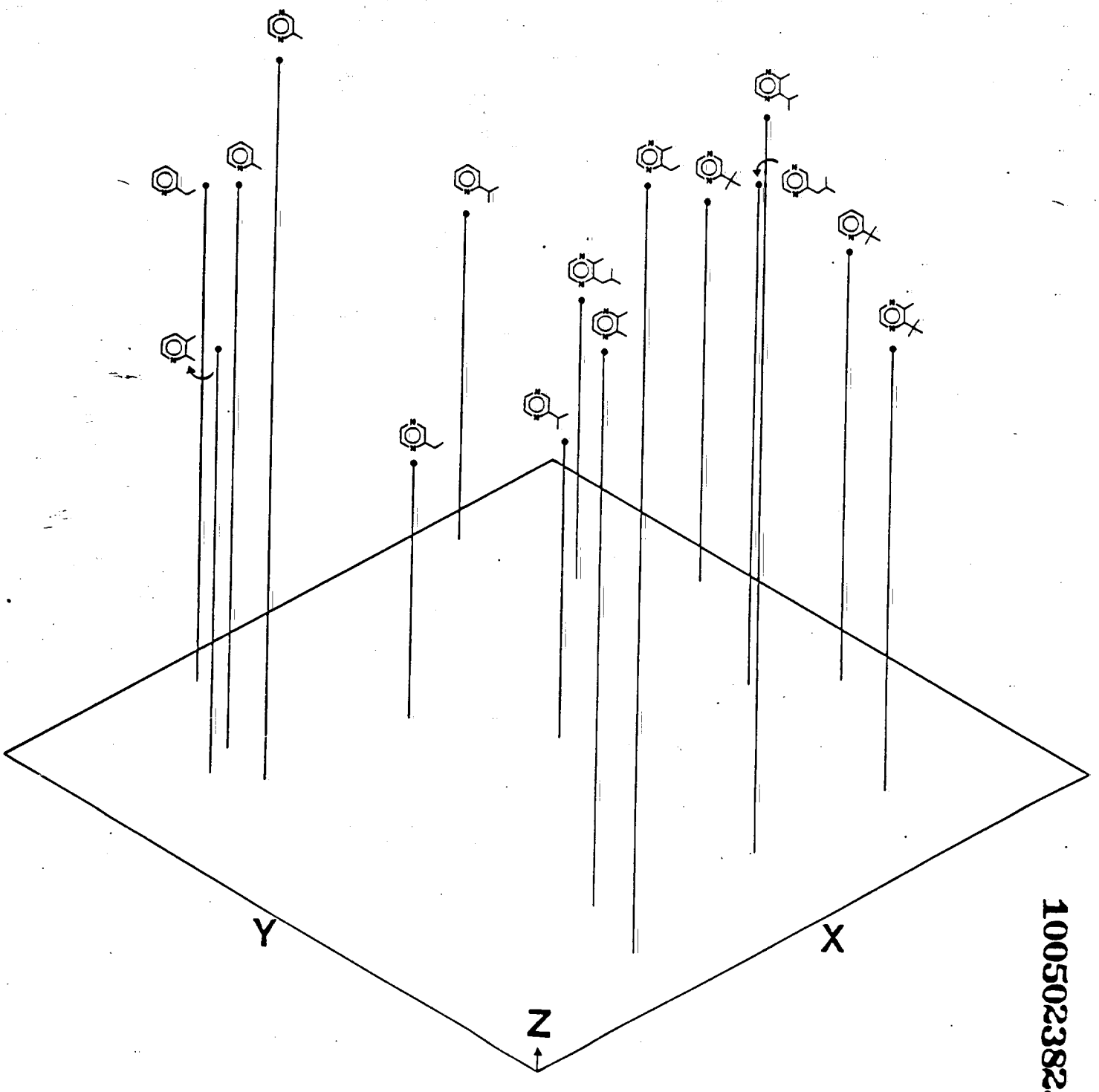


Figure 8b. Three Dimensional Space for MDS III.
x - y Projection.

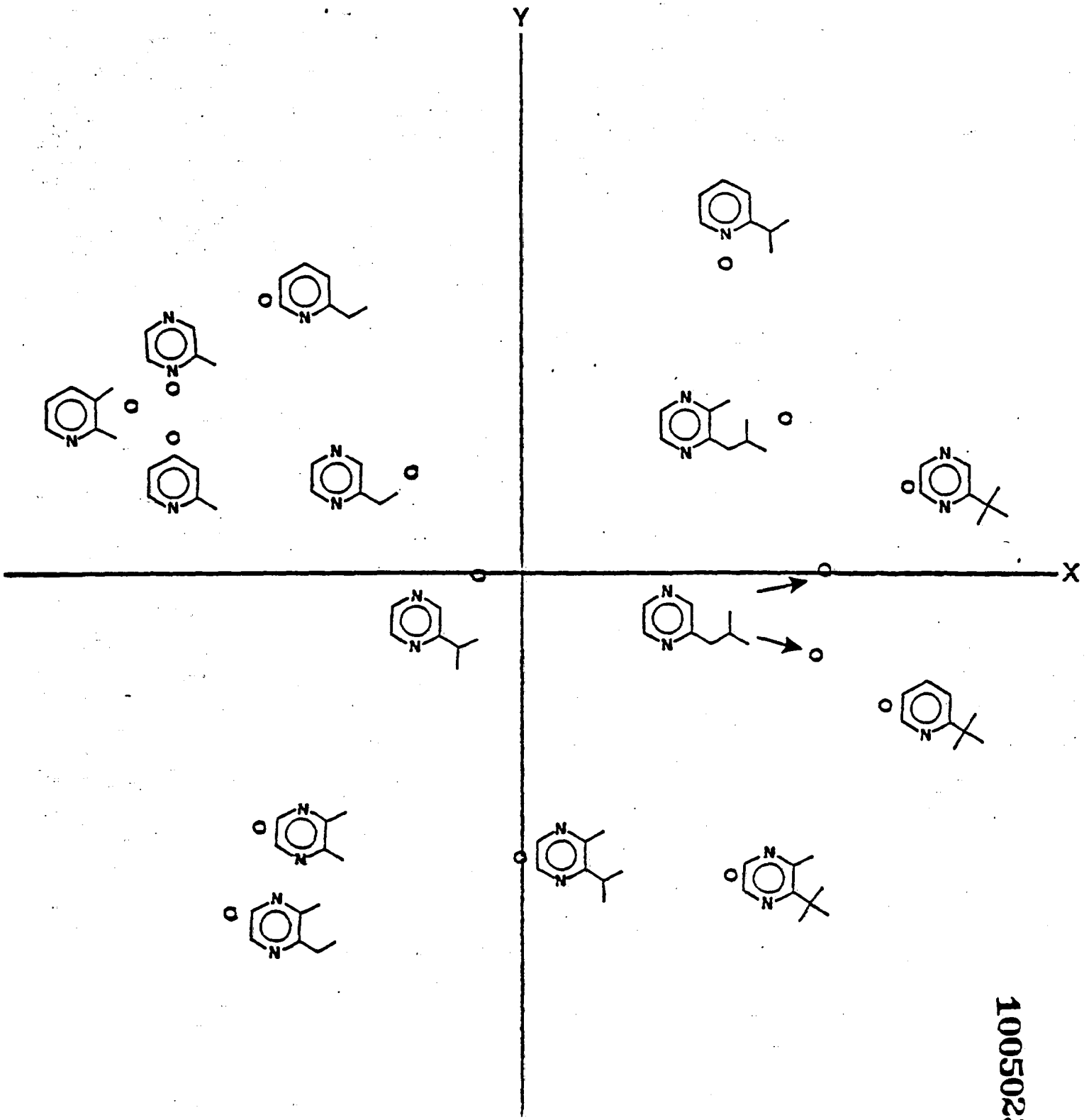


Figure 8c. Three Dimensional Space for MDS III.
x - z Projection.

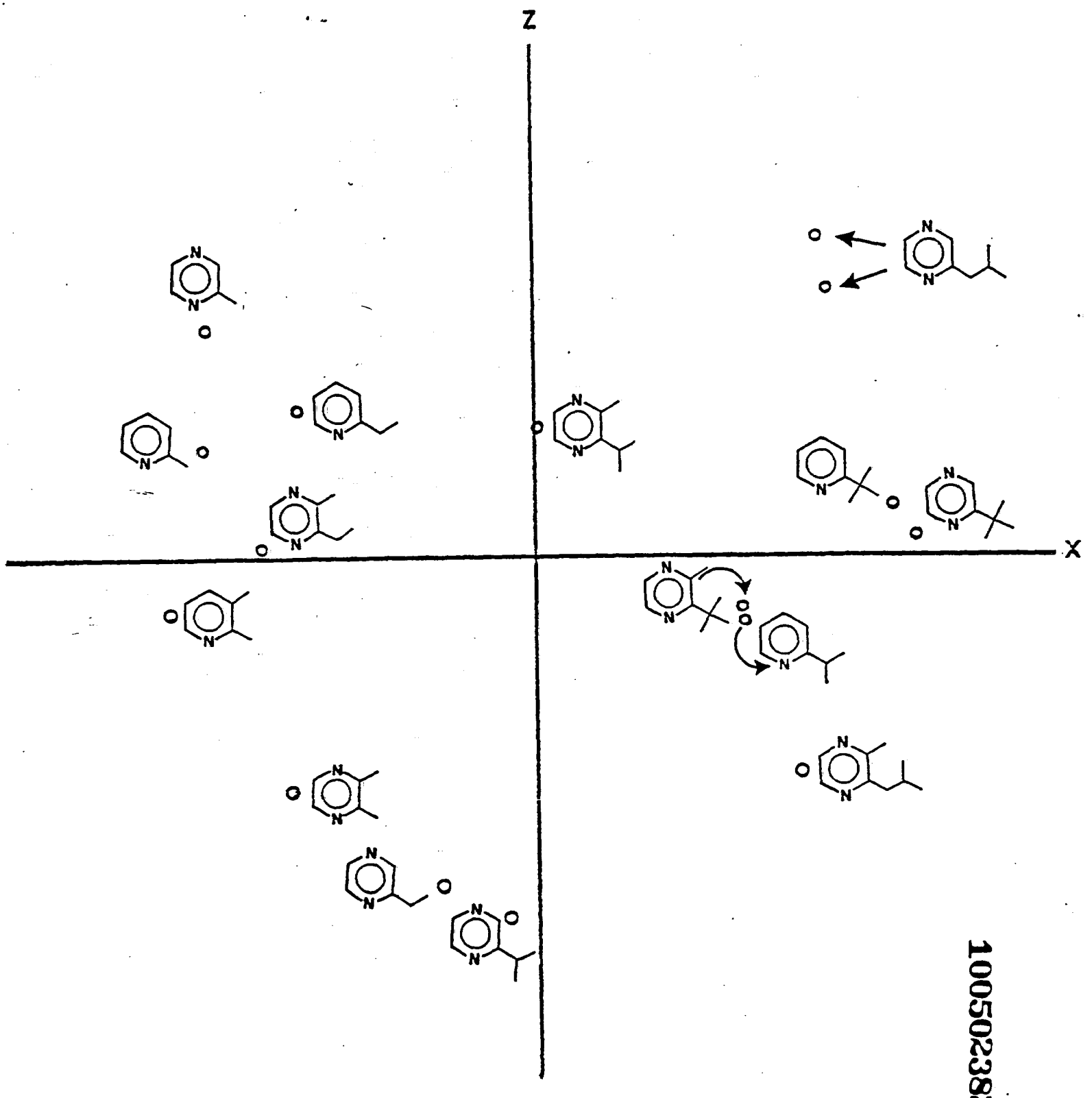


Figure 9. Molecular Weight Correlation for MDS III
(see eq. 7.)

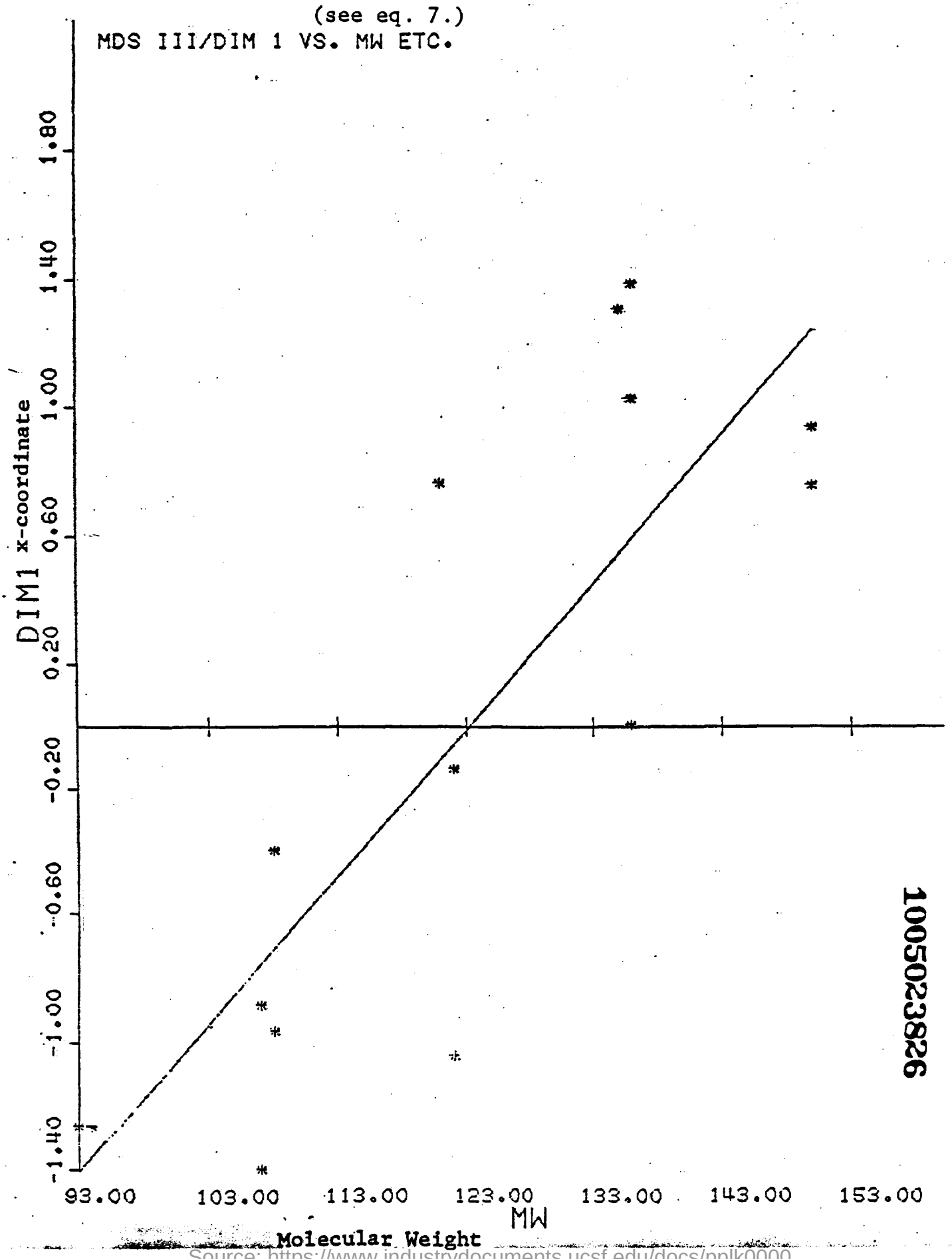
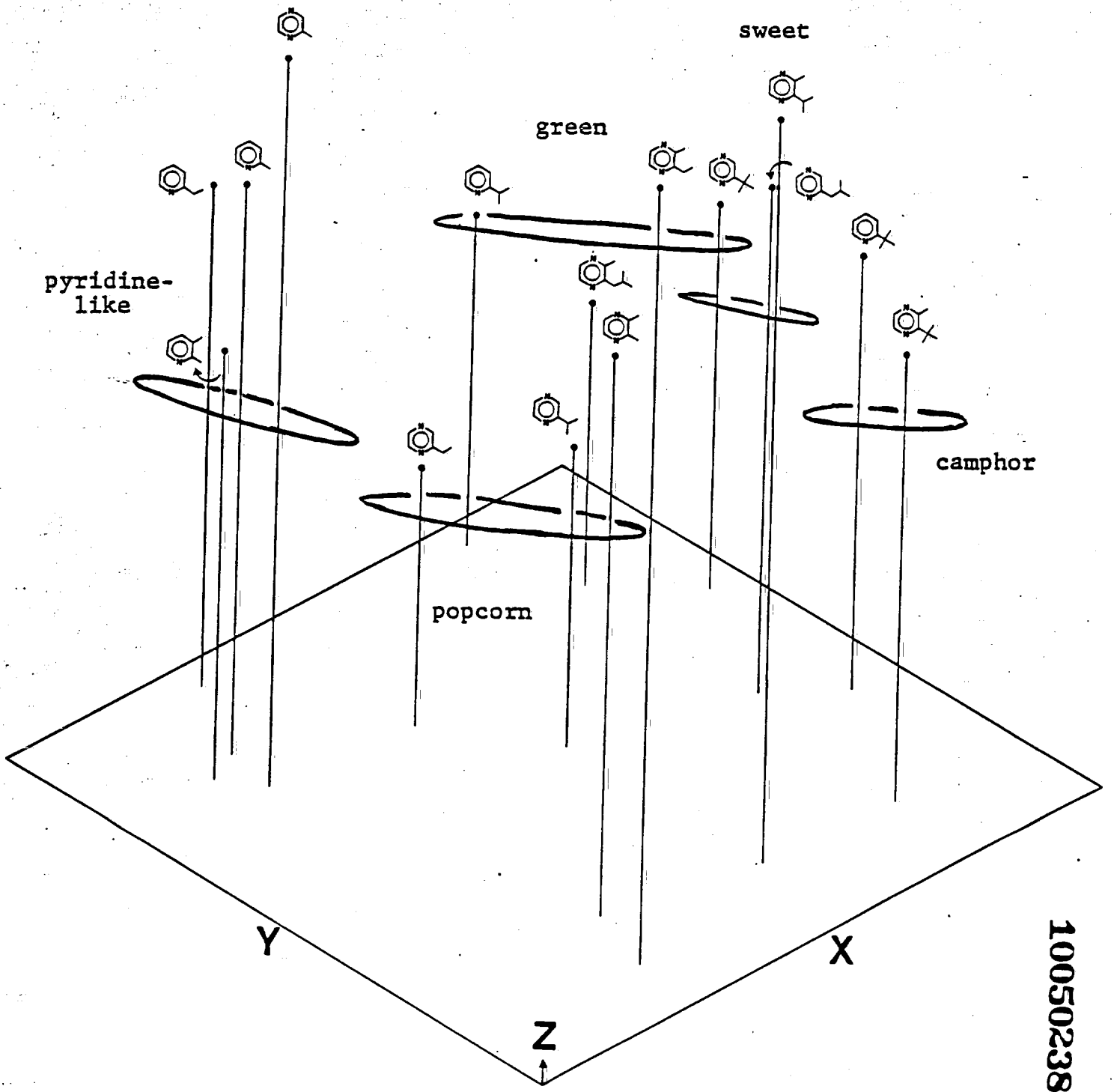


Figure 10 duplicates the MDS III dimensions but lists the odor descriptions given by the panelists (c.f. Table IV) for the stimuli. There is clustering in five locations: (a) pyridine-like; (b) popcorn; (c) green; (d) sweet; and (e) camphor. These descriptors were obtained previous to, and independent of, the multidimensional scaling data acquisition. Hence, we have not bastardized our non-semantic MDS experiment with descriptors. Nonetheless, we can now examine the MDS results in light of the independent descriptors. On a superficial basis, the clustering is to be expected if the MDS experiment has any validity -- since similar compounds should be placed in a similar location in the three dimensional space. However, we now have located in space five different odor qualitites relative to each other. This type of analysis may give us a handle to design odorants having overlapping subjective responses -- if we have a large enough data base.

One particularly interesting observation was made by several panelists during data collection for MDS III. When sniffing 2,3-dimethylpyrazine first, then 2-ethyl-3-methylpyrazine, they were not able to detect the latter. However, after resting for several minutes, they were able to detect the latter. When the evaluation was reversed, the same phenomenon was observed. This behavior is a manifestation of cross-adaptation, wherein both compounds are interacting with the same receptor site.

Structure-activity realtionship derivations and multidimensional scaling in odor research is in its infancy. Numerous questions regarding the MDS technique itself are being revealed in our research. What is the importance of intensity differences? Does

Figure 10. Three Dimensional Space for MDS III.
Odor Descriptions and Odor Spaces



1005023828

the presence of certain stimuli in a group affect the interrelationship among the other members of the group? When can spaces be overlapped? How dominating is the pleasantness/unpleasantness feature? What is the relationship, if any, between MDS spaces and odor profiling spaces? We are looking forward to answering some of these questions in the near future.

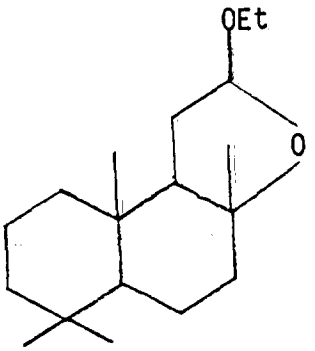
D. Isolation and Identification of Flavorants/Odorants[2]

Because there are other groups at R&D involved in flavor/odor isolation work, we intentionally minimize our efforts in this area. We become involved in isolation work when there is a particular chemical aspect which would benefit from our expertise.

An example of such an area is the characterization of flavorants which arise during the curing of Oriental tobacco. We reasoned that we could "chemically" simulate the curing process by reacting a "properly" chosen and commercially available precursor under the "appropriate" conditions to form materials which are naturally formed during the curing of tobaccos.

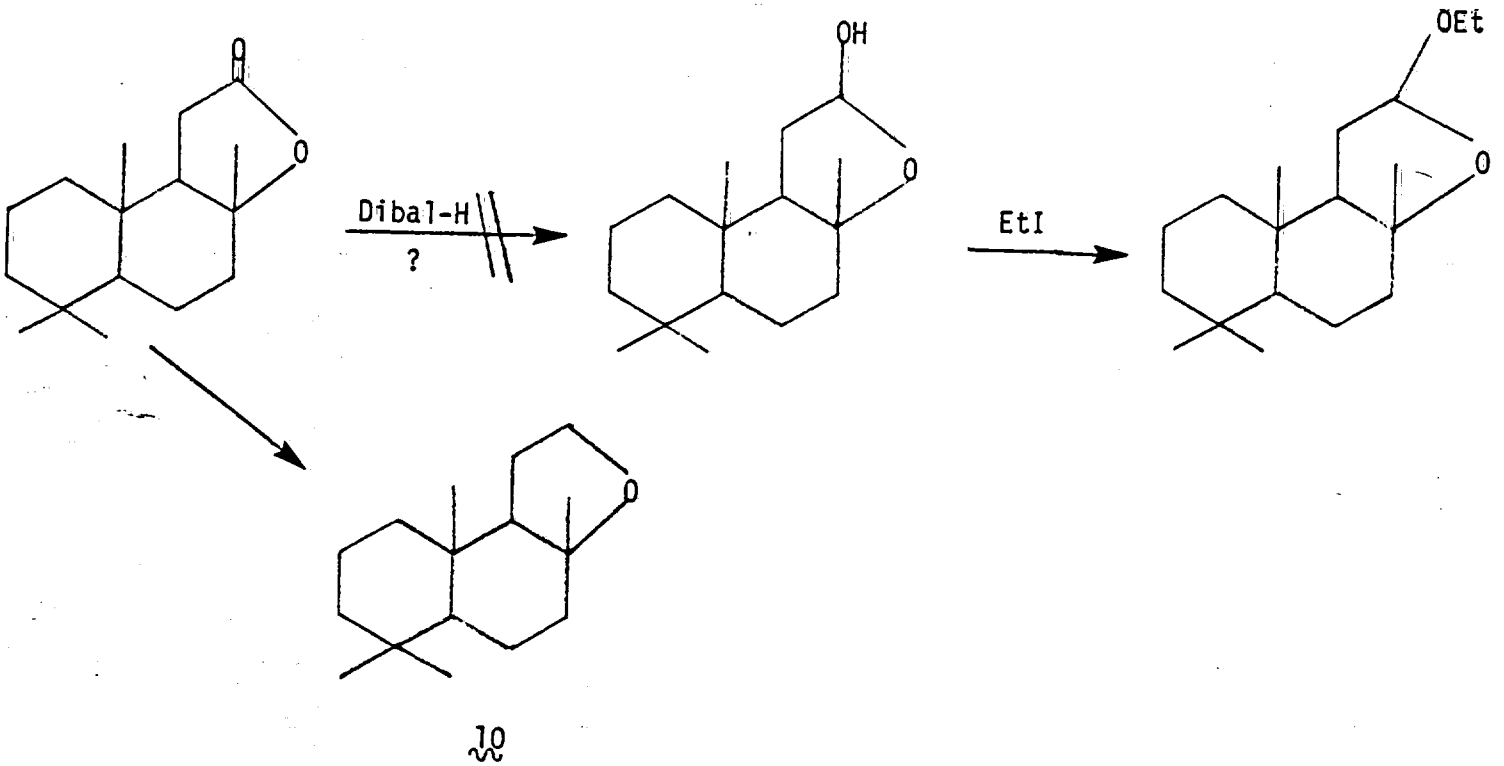
Abienol is a diterpene which has been reported in Oriental tobacco. During curing of Oriental tobacco, the abienol disappears suggesting that it may be the source of flavor compounds. The photo-oxygenation of abienol has been reported to give a large number of degradation products, but there has been no report of any flavor properties. We have subjected abienol to photo-oxygenation, and the resulting crude mixture was found to exhibit a dusty-woody aroma such as is present in cured Oriental Tobacco. Extensive fractionation by HPLC led to the isolation of several components, none of which had any odor. The odor was still present in the

mixture of minor components. This latter mixture was fractionally distilled using a Kugelrohr and the fraction with the woody odor was subjected to chromatographic separation, using HPLC and preparative gas chromatography. One component possessing a very interesting woody aroma was obtained in small quantity. Spectroscopic data (mass spectrum and NMR) led us to the tentative structure assignment of 9 for this material.



9

We have made one attempt to synthesize this compound by the following route. Unfortunately, the sole product from this reaction was the over-reduced ether 10 which was almost odorless. Before we attempt any further synthetic work, the structure assignment will be reevaluated by NMR analysis following installation of the 200 MHz NMR instrument recently purchased.



10

III. NICOTINE AND TOBACCO ALKALOID CHEMISTRY

A. Objective

There are eleven specific objectives that are addressed by the nicotine program, and these are as follows:

1. To develop a fundamental understanding of the mechanisms by which nicotine and other tobacco alkaloids interact with peripheral and central nervous system receptors *in vitro*.
2. To determine if nicotine analogues can be designed which exhibit differential *in vivo* activity, in particular, to separate out central nervous system responses from peripheral responses.
3. To determine if nicotine analogues can be designed which exhibit differential activity at different receptors *in vitro*.

4. To develop correlations between *in vitro* systems (e.g., receptor binding) and *in vivo* tests (*e.g.*, behavioral studies and rat blood pressure).
5. To assist the Behavioral Research group's efforts to delineate central and peripheral nicotinic effects; to examine the nature of reinforcement, effect on on-going behavior, etc.
6. To investigate the possible correlation of structural and chemical parameters with biological behavior.
7. To develop procedures to synthesize nicotine analogues and isotopically labelled nicotine analogues.
8. To perform, in a collaborative fashion, pharmacological testing of nicotine and its analogues with a goal of deriving structure-activity relationships.
9. To aid other groups with problems related to tobacco alkaloids (*e.g.*, to develop procedures for nicotine recovery from various manufacturing residues and effluents).
10. To establish PM's state-of-the-art participation worldwide in nicotine research so that PM's results can impact on external research.
11. To develop an effective insecticide(s) through collaborative testing of nicotine; in this conjunction, the mode of action(s) of these compounds will be investigated.

B. Overview of Synthetic Organic Chemistry

In order to achieve these objectives, effort is expended in a number of different areas: synthesis of optically active nicotine

analogues and of analogues in their racemic form; mechanistic studies aimed at evaluating reactivity, nucleophilicity, basicity, conformation and configuration; theoretical studies; and biological assays. This report will cover in detail the past year's results related mainly to our synthetic efforts.

During the past year, we have been involved in a number of synthetic projects which have been designed for two distinct segments of the program: (a) preparation of analogues for pharmacological testing and (b) synthesis of materials for use in the isolation and characterization of the nicotine receptor(s). Whenever possible, we have chosen our strategy such that the compounds prepared for (b) above can also be used for (a), and *vice versa*. In addition, we have designed our synthetic program to take advantage of synthetic technology developed in the synthesis of tobacco flavors which relate to pyridine chemistry, and *vice versa*.

The effort can be divided into the following areas:

Section III.C.1 Synthesis of Optically Active Nicotinoids

a. Resolution of Nornicotine, Anabasine and Related Analogues

b. Preparation of (-)-6-alkylnicotinoids

c. Preparation of (+)-Nicotine

Section III.C.2 Preparation of (-)-Nicotine-^{3}H

Section III.C.3 Preparation of Hydroxynicotinoids

Section III.C.4 Preparation of Nicotine Analogues

We note here some of the overlap in the above categorization. Many of the hydroxynicotinoids (III.C.4) are optically active (III.C.1) and were designed to be so. The 6-alkylnicotinoids

(III.C.1) could be described in Section III.C.4. Thus, the organization of this report was designed for pedagogical simplicity.

C. Synthetic Studies

1. Resolution of Optically Active Nicotinoids

The preparation of optically active nicotinoids is a particularly important and challenging problem. It is clear that biological properties are very dependent on chirality, and enantiomers show differences in both *in vivo* and *in vitro* tests. Significantly, racemic mixtures do not always show a result equal to the average of the individual enantiomers; effects such as antagonism, both competititve and noncompetitive, can and often do occur.

In order to develop a biological testing program of the highest caliber, it was necessary to obtain a wide range of nicotinoids in their optically active forms. For maximum flexibility and efficiency, we desired a method of nicotine resolution which is (1) applicable to as many analogues as possible, including nornicotine analogues; (2) affords both enantiomers (C-2' position of nicotine is chiral); and (3) produces these enantiomers in the same step, thereby avoiding either asymmetric destruction techniques or classical "enhancement of activity" techniques.

In addition, as we have become more sophisticated in our testing program, we have developed a keen appreciation for the need to study the nicotine receptor(s). These receptors are the macromolecular components of tissue(s) to which the nicotinoids bind. The interaction or binding of the agonist with the receptor in turn initiates a pharmacological response. Consequently, the more we

know about the receptors involved in the activities we are interested in, the more we will know about our system and the more likely we will be able to control it.

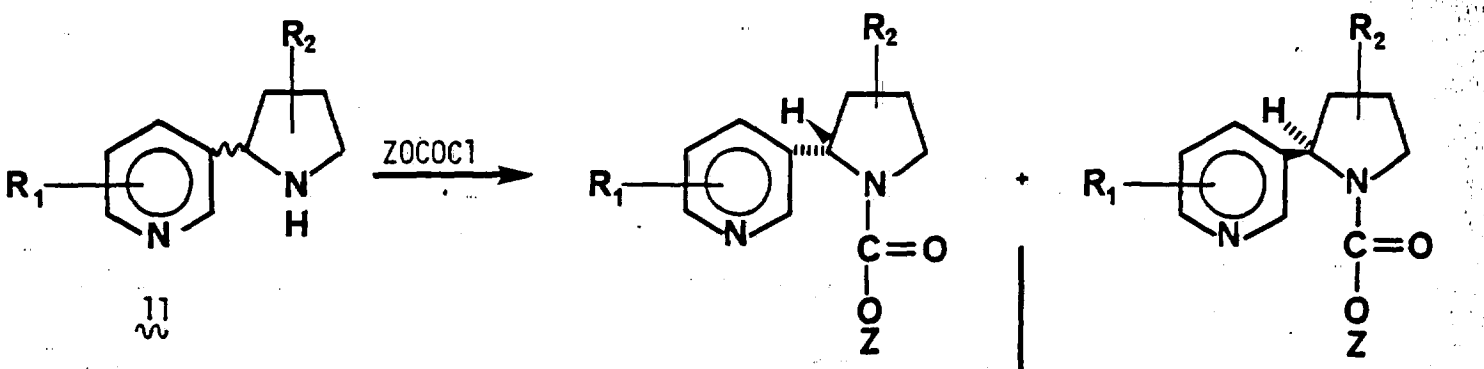
To this end, we have interest in defining the location of the nicotine receptor(s). This is being done in two fashions: by behavioral pharmacological techniques (V. DeNoble) and by receptor binding studies, including affinity chromatographic isolation of rat brain CNS receptors. An important, perhaps essential aspect of binding studies, is the use of optically pure tritiated (-)-nicotine. To date, the only tritiated nicotine available has been racemic, i.e., (±)-nicotine-^{3}H. Consequently, we undertook the synthesis of optically pure tritiated nicotine; i.e., (-)-nicotine-^{3}H. Since we did not wish to carry out a tritium synthesis here at PM, it was sufficient to design the synthesis using, if necessary, deuterated reagents rather than tritiated reagents.

It was important for us to learn that the commercial synthesis of tritiated d,ℓ-nicotine involves the alkylation of d,ℓ-nornicotine with tritiated halomethane. Thus, we placed as a high priority the synthesis of optically pure (-)-nornicotine.

a. Last year (Accession No. 81-078), we discussed in detail the preliminary results of our efforts to resolve d,l-nornicotine into its optically pure enantiomers. We had, at that time, succeeded in the analytical separation of the nornicotine-menthol urethane diastereomers, discussed in the following paragraphs.[5] Unfortunately, we had not achieved a preparative scale purification of these diastereomers, rendering our success more academic than practical. Because of difficulties

in achieving preparative purifications, we abandoned this approach and focused our efforts along other lines, which were in themselves successful (c.f., Section III.C.2). However, we felt that the urethane approach had the most potential -- and was the only procedure which would furnish both enantiomers. Hence, we returned to this project and its successful completion will be described in the following paragraphs.[5,6]

The successful strategy is illustrated in Scheme IV where "Z" represents the levorotatory enantiomer of menthol, i.e., ℓ-menthol. The procedure used is as follows: d,l-nornicotine (d,l-11, $R_1 = R_2 = H$) is converted to a urethane of ℓ-menthol by treatment with ℓ-menthyl chloroformate. This urethane is a 50:50 mixture of two diastereomers (see Figure 11) and was separated into its significantly enriched components by HPLC techniques. Figure 12 displays one HPLC chart for the separation of 300 mg of the diastereomeric mixture using a Whatman Magnum-20 Column. Each of these resolved diastereomers was hydrolyzed independently in 10% HCl at 110° for 3 days in a high pressure reactor to give, following distillation, (-)-nornicotine and (+)-nornicotine having the highest optical rotations reported for these compounds to date. We now have ca. 200 mg of each nornicotine enantiomer and ca. 1.5 g of each purified diastereomer.[5-7]

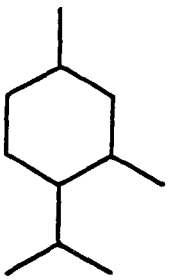


HPLC Separation

(+)-nornicotine urethane (-)-nornicotine urethane

(+)-nornicotine (-)-nornicotine

Z=



Scheme IV

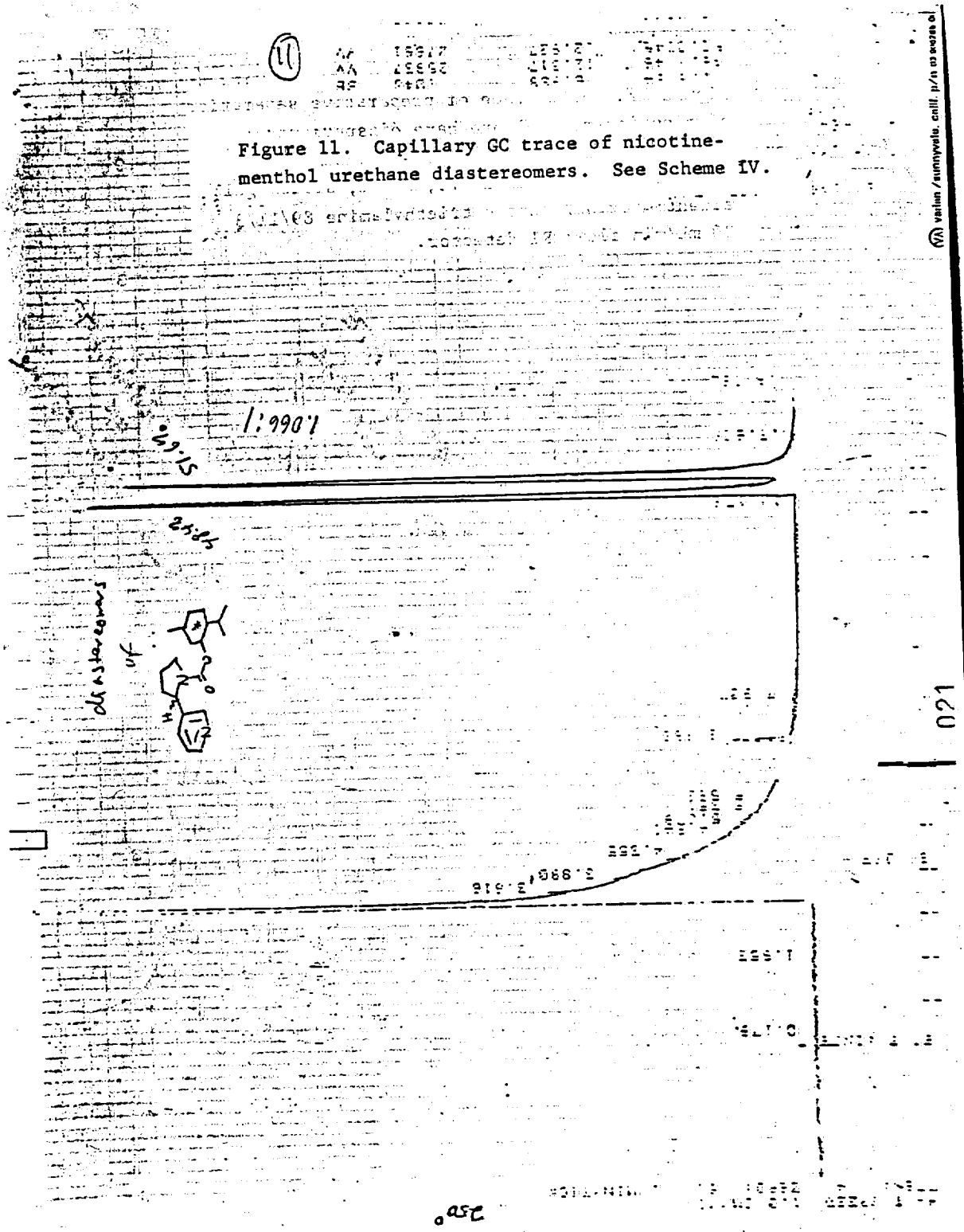


Figure 11. Capillary GC trace of nicotine-menthol urethane diastereomers. See Scheme IV.

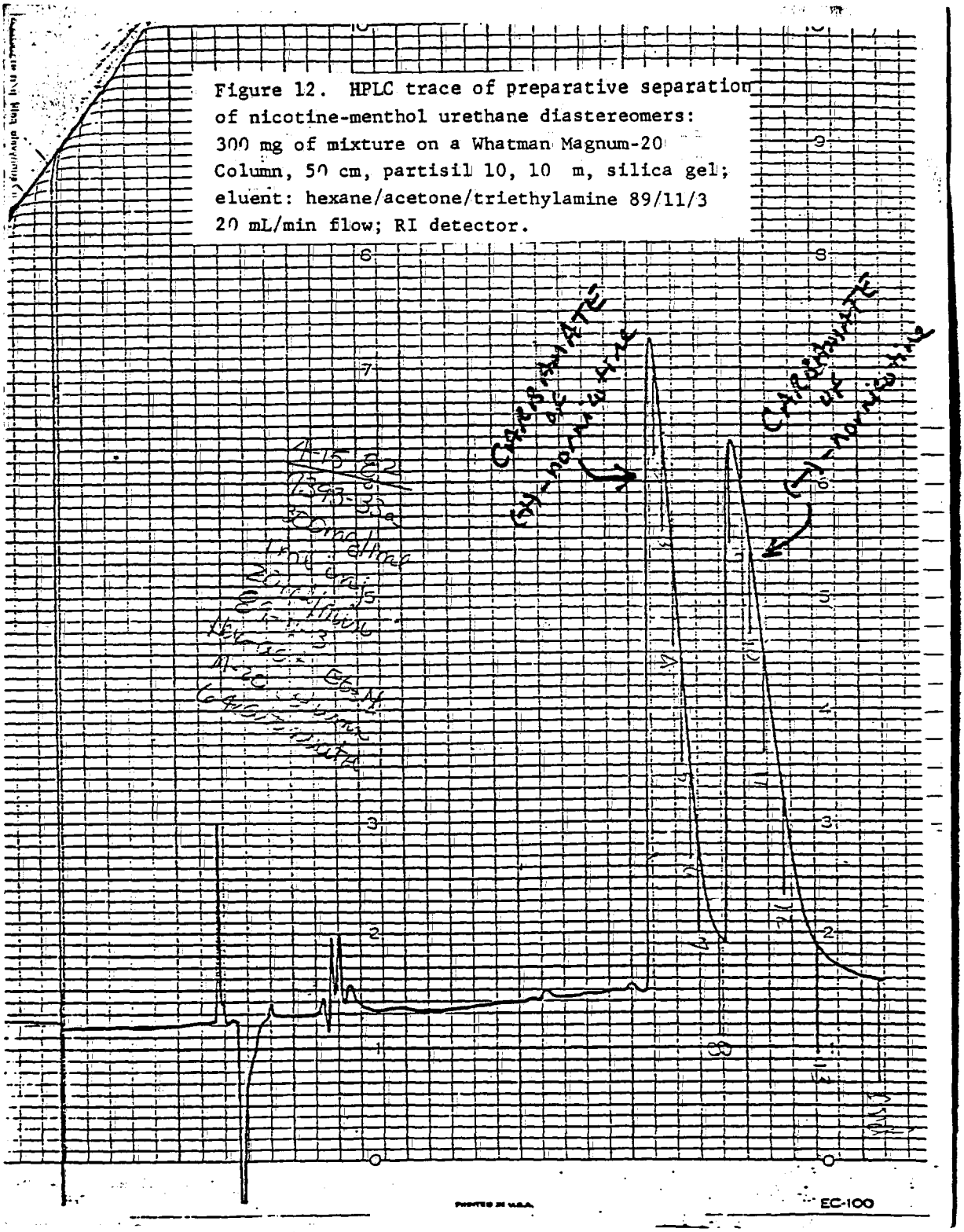
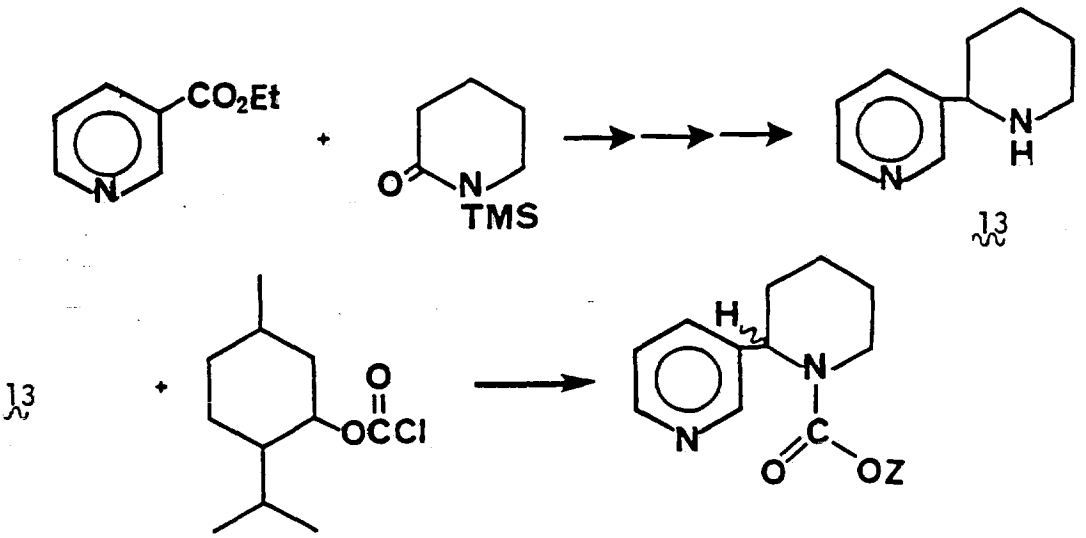


Figure 12. HPLC trace of preparative separation of nicotine-menthol urethane diastereomers: 300 mg of mixture on a Whatman Magnum-20 Column, 50 cm, partisil 10, 10 m, silica gel; eluent: hexane/acetone/triethylamine 89/11/3 20 mL/min flow; RI detector.

We have been applying this procedure for the preparation of the enantiomers of anabasine (13) and of the most simple chiral nicotine analogue, N,N-dimethyl-1-(3-pyridyl)ethylamine (14). We prepared d,l-anabasine using standard procedures from N-trimethylsilylpiperidinone and ethyl nicotinate, as shown in Scheme V, and converted it to its menthyl urethanes. We were very disappointed to find that these urethanes failed to separate under the conditions (Figure 12) which worked so successfully for the nornicotine case. However, we recently have designed alternative HPLC conditions which separate the anabasine urethanes and we shortly will be performing the purification on a preparative scale.[5-7]

Scheme V

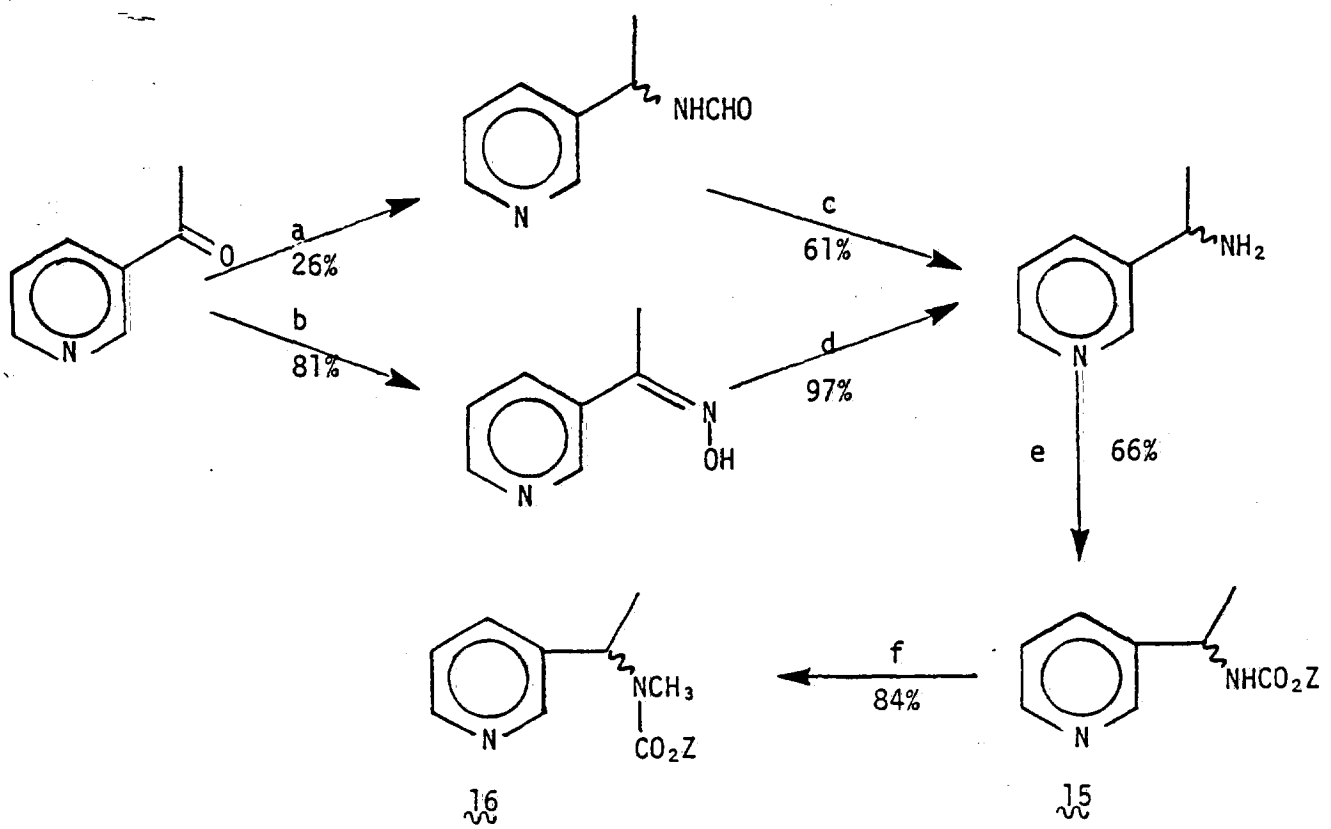


An additional utilization of this HPLC purification scheme is the determination of the optically purity of secondary (or primary) amines. For instance the optical purity of natural anabasine and anatabine is unknown. We have taken anabasine isolated from tobacco and converted it to its menthyl urethanes.

In preliminary experiments, GC analysis (similar to that in Figure 11) indicates the presence of two compounds in *ca.* 90:10 proportions. We are in the process of standardizing our quantitation and anticipate that we will be able to establish the optical purity of anabasine soon.[5]

Scheme VI indicates the progress we have made to date regarding the preparation and resolution of N,N-dimethyl-1-(3-pyridyl)-ethylamine (14). Unfortunately, we have not been able to resolve the urethane mixture of either 15 or 16.

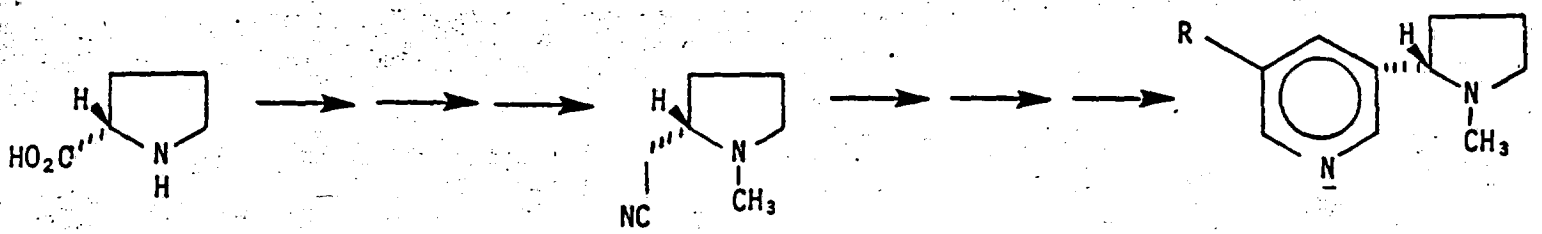
Scheme VI



(a) $HCONH_2$, HCO_2H, (b) NH_2OH, (c) HCl (d) H_2/Pd-C (e) menthylchloroformate, (f) CH_3I/NaH.

This year, we have completed our asymmetric synthesis of optically active (-)-nicotine and (-)-5-methylnicotine from commercially available proline (eq. 8).[5,6] Two particular achievements not previously discussed are as follows: (i) We have converted proline to the nitrile 17, the key intermediate in this synthesis, using a procedure which increases the optical yield of the entire sequence by 100%. This provides nicotinoids in 56% e.e.

(8)



R=H, CH_3

17

(ii) Together with Ron Bassfield, we have developed an nmr technique which affords resolution of some of the enantiotopic protons in d,l or partially racemized nicotinoids. This involves the use of a chiral shift reagent, $Eu(tfac)_3$. Interestingly, we had some time ago attempted such a procedure but failed because we had not used a very large excess of shift reagent, as in the current experiments. To date, we have analyzed nicotine, 5-, and 6-methylnicotine using this technique.[5]

b. Preparation of Optically Active 6-Alkylnicotinoids

6-Substituted nicotinoids are of particular interest because of our observation that 6-methylnicotine is as active as nicotine in a number of bioassays and, in fact, more active than nicotine in some tests. These compounds are also proving to be of value as

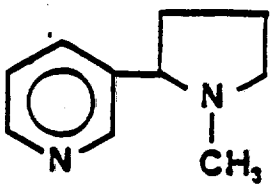
intermediates in the preparation of affinity binding agents and suicide nicotinic agonists also (see discussion below, Section III.C.3).

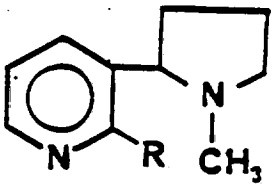
The procedures discussed above were designed to be applicable to the preparation of both enantiomers of nornicotine and nicotine analogues as well as the parent compounds. For certain biological tests and procedures (*e.g.*, development of affinity adsorbants for nicotine receptors), we decided to prepare nicotine analogues directly in optically active form. If possible, synthesis from commercially available, optically pure nicotine should be efficient, simple, and direct. In all cases, it would be necessary to establish the degree of optical purity obtained. This last factor of course would apply to any procedure aimed at obtaining optically active compounds.[5]

Last year, we reported that we could obtain mixtures of 2-methylnicotine (18a), 4-methylnicotine (19a), and 6-methylnicotine (20a) (c.f. eq. 9) from the reaction of nicotine with methyllithium. We were able to separate the methylnicotines from each other by HPLC techniques.[5,6] We have continued to apply these alkylations to other alkyllithiums, thereby preparing other alkylnicotinoids as shown in eq. 9. Unfortunately, the optical purity of some of the alkylnicotinoids prepared in these reactions is low.[5]

Table VIII lists the compounds prepared by the reaction of nicotine with alkyllithium reagents and with alkyl radicals the latter to be discussed below. When possible, we have isolated the unreacted nicotine and have obtained its optical rotation, thereby allowing us to derive information regarding the mechanism of the racemization of the alkylated product. In all cases except for the nicotine-tert-butyllithium reaction, the recovered nicotine was optically pure, indicating that the racemization takes place either during the alkyllithium reaction or following the reaction.[5] See Scheme VII.

RLi +

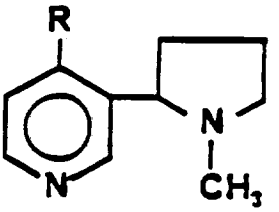




18

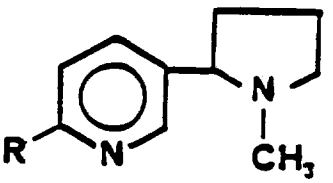
(9)

+



19

+



20

a, R=CH_3

b, R=Et

c, R=i-Pr

d, R=c-Pr

e, R=Bu

f, R=sec-Bu

g, R=t-Bu

h, R=vinyl

TABLE VIII

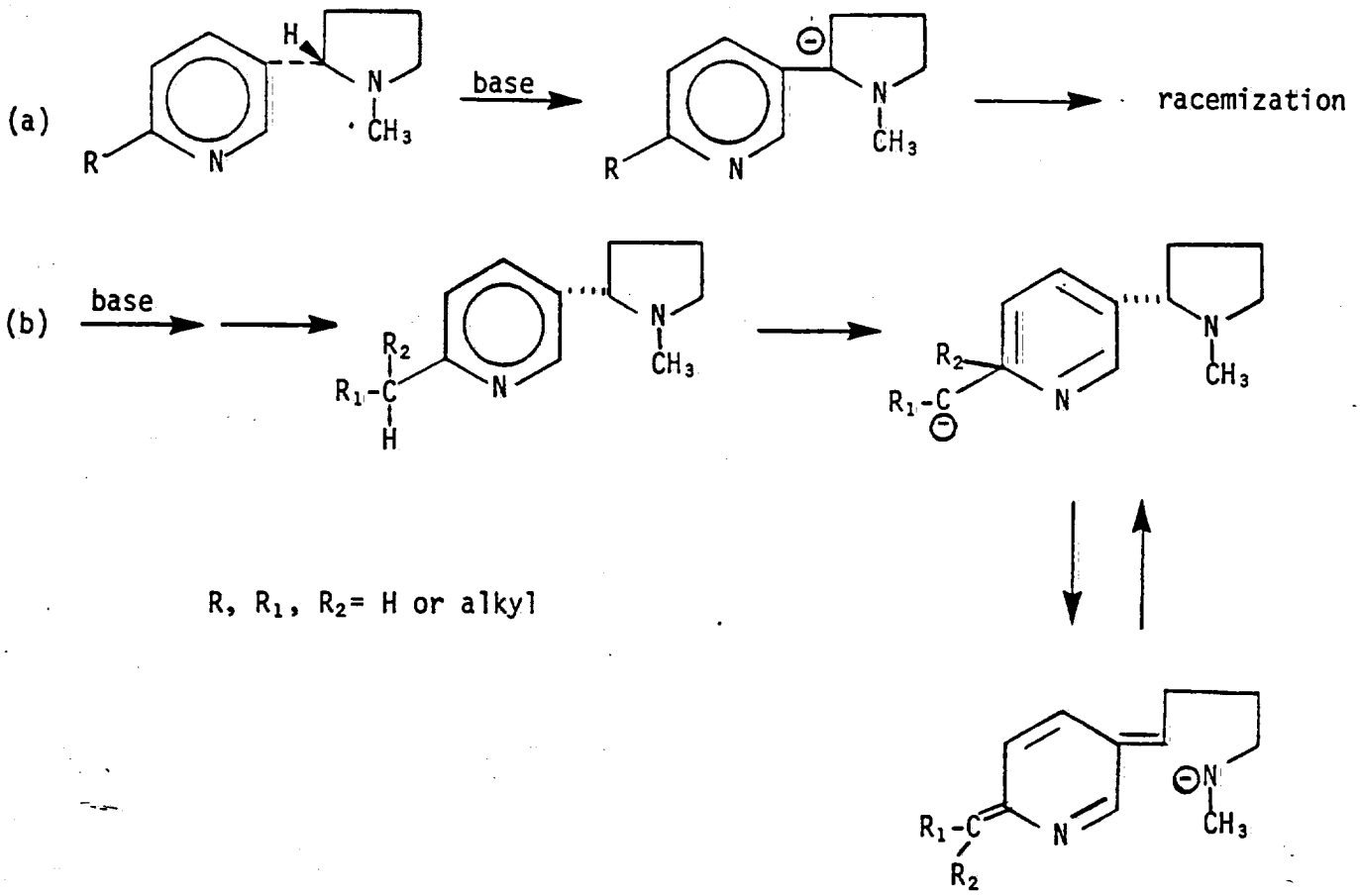
Preparation of 6-Alkylnicotinoids[5]

		Alkyllithium Reactions			Alkyl Radical	
Entry	R	$[\alpha]_D^{20}$ of Product	$[\alpha]_D^{20}$ of Recovered Nicotine	Yield (%)	$[\alpha]_D^{20}$ of Product	Yield (%)
1	Ethyl	-160°	-169°	30	-151°	28
2	Pr	-	-		-155°	30
3	i-Pr	-17°	-	60	-149°	17
4	c-Pr	-38°	-	17	-168°	13
5	Bu	-12°	-170°	43	-	-
6	sec-Bu	-30°	-	28	-	-
7	t-Bu	-30°	-42°	33	-146°	42
8	Vinyl	-58°	-150°	6	-	-

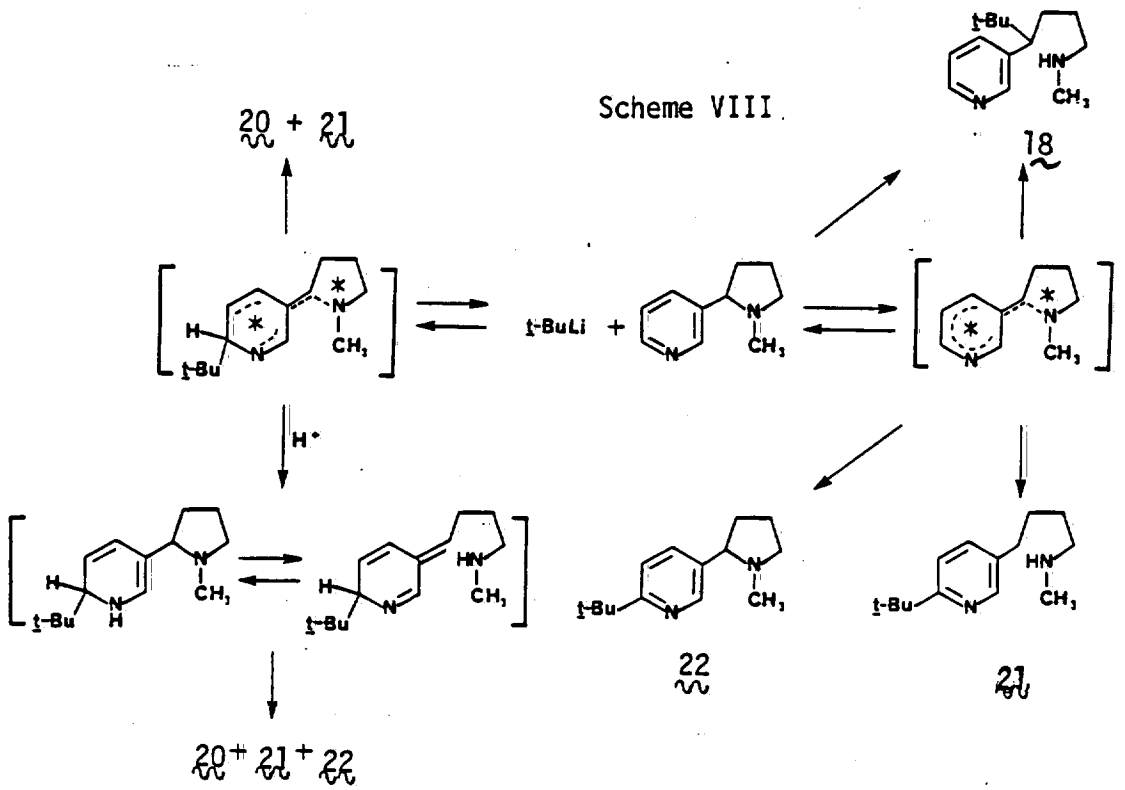
We have excluded both racemization mechanisms suggested in Scheme VII in the following fashion. We reacted nicotine-2'-d_1 with methyllithium and tert-butyllithium under the appropriate reaction conditions; the unreacted and reisolated nicotine showed full retention of the original of deuterium incorporation. Second, we treated optically active (-)-6-methylnicotine with one equivalent of methyllithium for three and for ten hours in refluxing toluene as well as with LDA/THF; the recovered (-)-6-methylnicotine had the same optical rotation, and hence optical purity, as the starting substrate, again indicating no racemization.[5,6]

Based on the above two types of experiments, we conclude that the racemization occurs during the alkylation reaction itself. We propose a set of mechanisms shown in Scheme VIII for tert-butyllithium. We emphasize that radical transfer is more likely in the case of tertiary alkyllithiums and purely carbanionic mechanisms may be obtained for the other organolithium reactions. Further proof of the viability of this mechanism was the isolation of seco-products 21 and 22 (i.e., ring cleaved products) in the tert-butylations.

Scheme VII

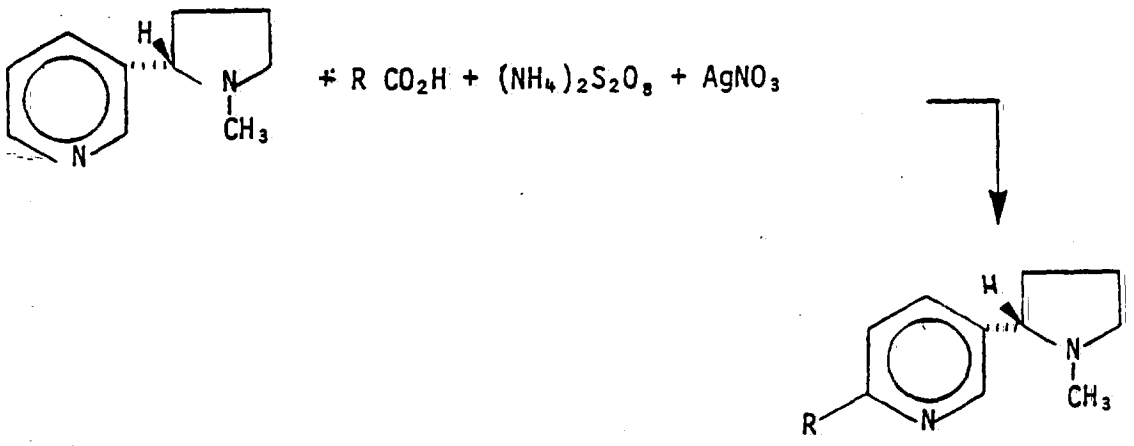


Scheme VIII



Because the alkyllithium reactions led partially to racemized 6-alkylnicotinoids, we were desirous of finding another possible direct route to this class of compounds. We had some experience with the reaction of methyl radical with nicotine which resulted in the formation of optically pure 6-methylnicotine (and 2-methyl and 4-methylnicotine as well).[6] Since we felt that it was far less likely that racemization would occur in radical reactions, we undertook an examination of the reaction of nicotine with various alkyl radicals. The overall reaction is shown in eq. 10, and the results of our experiments are shown in Table IX.[1]

(10)



Rather than leave the impression that these free radical reactions are without complications, we illustrate the complexities of reagent:nicotine ratio and reaction conditions on product yield in Table IX.

c. Preparation of (+)-Nicotine

We have continued to obtain the (+)-nicotine necessary for other experiments with the contributions of Dr. Bob McCuen. The process involves selective microbial destruction of (-)-nicotine in (±)-nicotine mixtures. To facilitate this procedure, we have now prepared (+)-nicotine from (-)-nicotine in one step rather than

TABLE IX[1]

Preparation of 6-Alkylnicotinoids, via Free Radical Process (c.f. Eq. 10)

Radical	Nicotine	RCO_2H	$(NH_4)_2S_2O_8$	Reaction Time: Heating Time	Reaction Time: Cooling Time	% Recovered[(d)]	Nicotine (%)	2-(%)	4-(%)	6-(%)	Other (%)
t-Bu	1	5	2.5	35 min	0	3.7g	~2	-	~2	>90	-
isopropyl	1	5	2.5	45 min	1 hr	3.8g	~10	trace(?)	<5	~80	<2
cyclopropyl	1	5	2.5	90 min	1 hr	-	>90	-	<2	trace	<5
cyclopropyl	1	5	5	4 hr	overnight	2.2g[a]	~8-10	~5	~8-10	~50	~20
ethyl	1	5	2.5	75 min	1 hr	2.2g[a]	~70	~5	~10	~5	~7-10
ethyl[b]	1	5	5	3.5 hr	overnight	2.8g[a]	~5	trace	~10-15	~50	~10
ethyl	1	5	5	5 hr	overnight	-	trace	-	~40	~5	~50
ethyl[c]	1	5	5	3 hr	1 hr	-	trace	-	~30	~10	~50
ethyl[c]	1	5	5	1 hr	1 hr	3.6g[a]	10	3	12	45	~25
n-propyl	1	5	5	4 hr	overnight	3.75g[a]	<5	-	~5	~10	~80
n-propyl[c]	1	5	5	1 hr	1 hr	4.2g[a]	14	4	10	42	~25

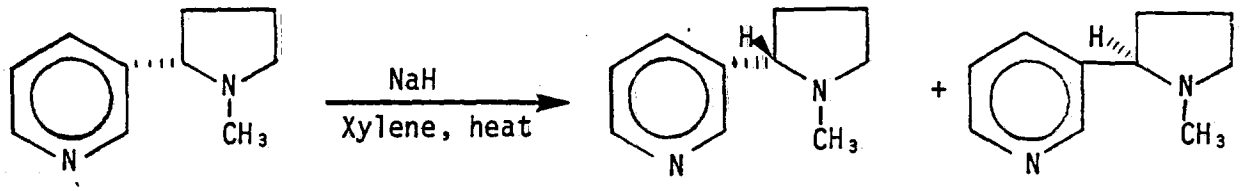
(a) distilled

(b) not reproducible q

(c) $(NH_4)_2S_2O_8$ (aq) and RCO_2H added simultaneously

(d) all reactions used 5g nicotine scale

the multistep sequence from N-trimethylsilylpyrrolidinone and ethyl nicotinate (eq. 11). We have also established the mechanism for this racemization, namely abstraction of nicotine's C-2' hydrogen atom by examining the same reaction with nicotine-2'-d_1.[5,6]

(11) 

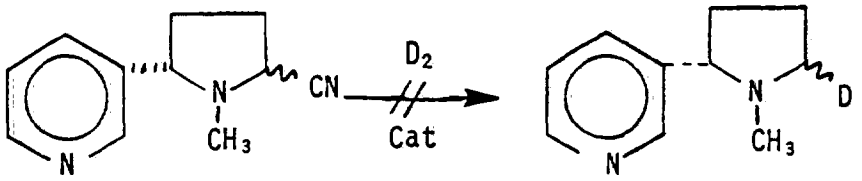
23

2. Preparation of (-)-Nicotine-^{3}H

In Section III.C.1.a, we discussed in detail our needs for (-)-nicotine-^{3}H and our successful preparation of (-)-nornicotine and (+)-nornicotine. We anticipate no difficulty in transforming (-)-nornicotine to (-)-nicotine-^{3}H having large specific activity (60-80 Ci mmol^{-1}) and with complete retention of configuration.

We have also investigated two other procedures for the preparation of (-)-nicotine-^{3}H and report on these in this section. First, and least successful of all our methods, was the catalytic reduction of 5'-cyanonicotine (23) to nicotine. We reasoned that the optically pure 23 could be reduced to nicotine without loss of

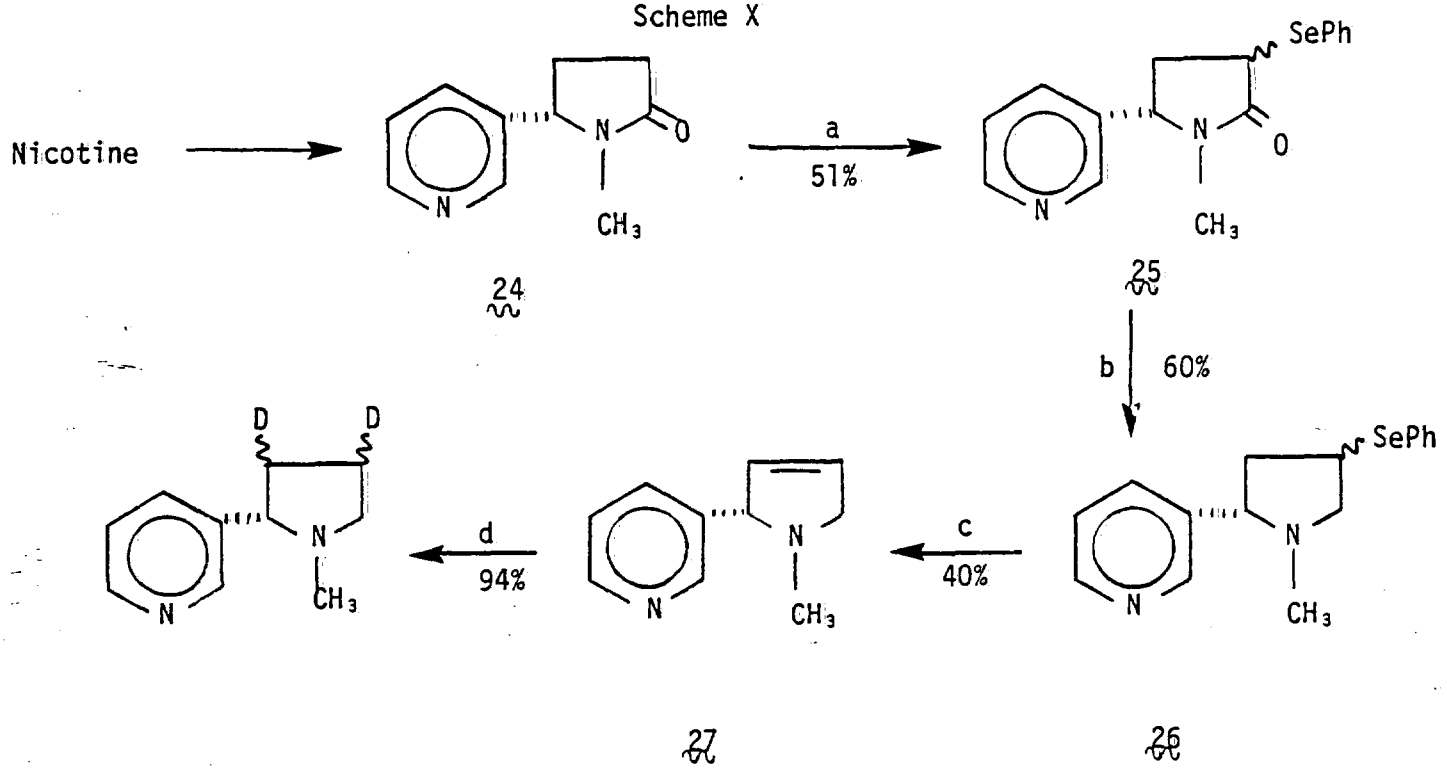
optical purity. We examined a number of reducing agents, and although we were able to obtain nicotine from the reaction (eq, 12), the yields were low, and this route was abandoned.[6]

(12) Nicotine → 

23

A more indirect route involved the reduction of a dehydronicotinoid. Ultimately, this strategy would require the reduction to be carried out with tritium gas, a very reasonable process to perform experimentally. Scheme X summarizes our work in this area. Nicotine can be transformed without loss of optical purity to cotinine (24). The lactam 24 was then functionalized at the C-4' position with phenylselenyl chloride, thereby incorporating a functionality which could be eliminated to form the requisite olefin. To that end, the functionalized lactam 25 was reduced without difficulty to 26. The dehydronicotine 27, also known as dihydronicotyrine, was obtained by oxidation of 26 and subsequent elimination. A wide variety of reducing conditions were examined to form nicotine from 27, the best being 5% Pd/C which gave nicotine in 94% yield, 86% enantiomeric excess. See Table X for additional details.[6]

Scheme X



24 25 26 27

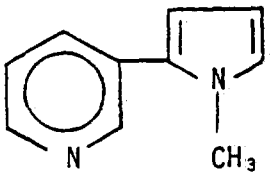
(a) LDA followed by PhSeCl, (b) B_2H_6, (c) 30% H_2O_2, (d) 5% Pd/C.

TABLE X

Hydrogenation/Deuteration of 3',4'-Dehydronicotine[6]

Entry	Catalyst/Conditions w/EtOH	% Conversion
1	D_2-5% Rh/C, 15 psi, 22 hr	22% nicotine, 2% nicotyrine
2	D_2-RuO_4, 15 psi, 21 hr	4% nicotine, 0.5% nicotyrine
3	D_2-PdO, 5 psi, 2.5 hr	1% nicotine, 15% dihydro-metanicotine 24% nicotyrine
4	D_2-5% Pd/C, 5 psi, 1 hr	58% nicotine, 1% dihydro-metanicotine, 21% nicotyrine
5	D_2-5% Pd/C, 5 psi, 4-5 hr, presaturation w/D_2 (15 min)	91% nicotine, 5% nicotyrine

During the course of these reactions, it became clear that a major stumbling block was a shortage in the availability of 27. We sought a simpler route and decided to prepare d,l-27, as shown in eq. 13.

(13) nicotine $\xrightarrow[\text{Pd/asbestos}]{\Delta}$  $\xrightarrow[\text{HCl}]{\text{Zn}}$ 27

28

Preliminary results indicate that 27 is very active in a number of behaviorial tests and we are examining it further.

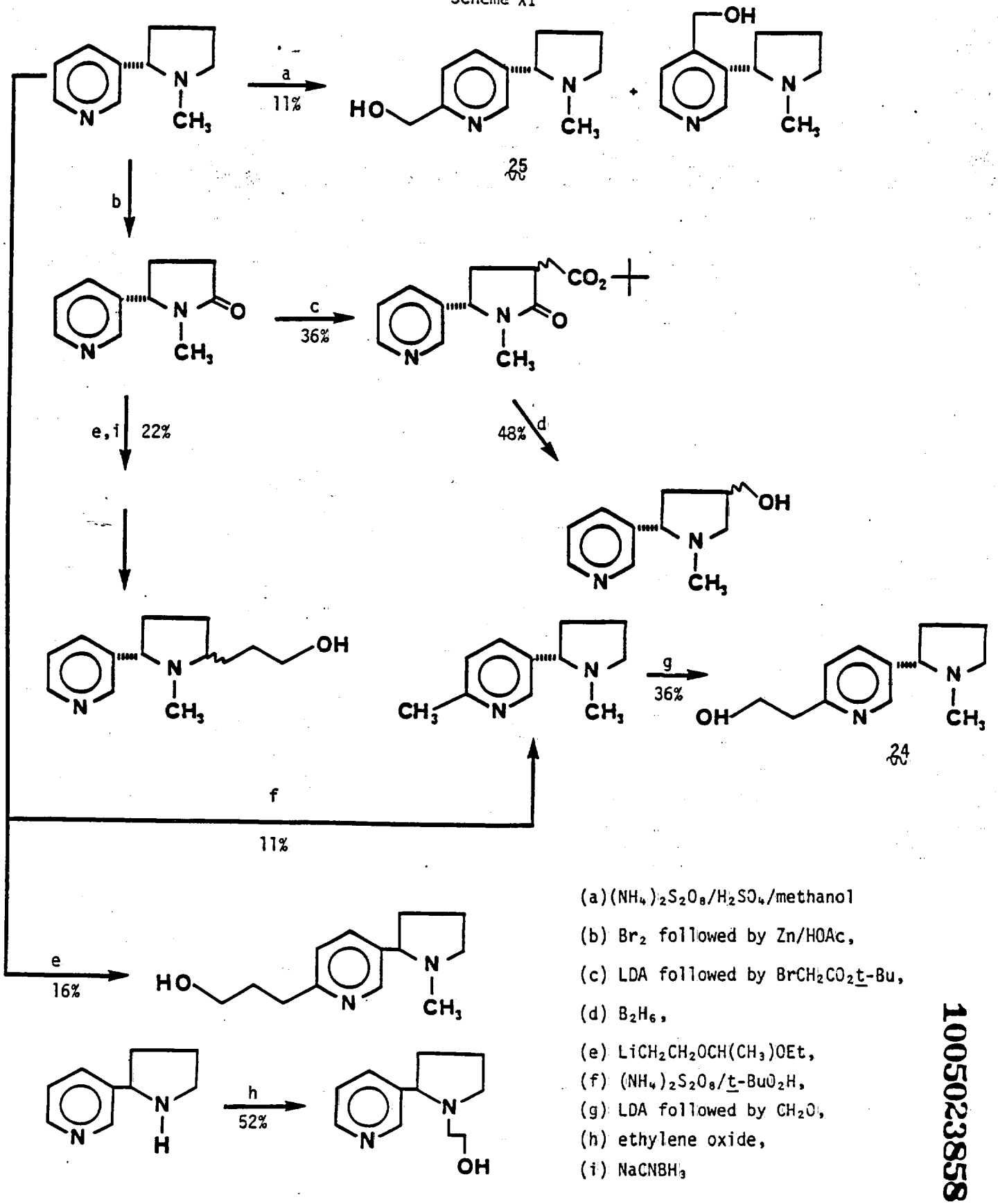
3. Preparation of Hydroxynicotinoids[5,6]

We have spent a considerable effort during the last year preparing a variety of nicotinoids having a hydroxy substituent. Our major incentive for this work was to prepare a ligand for a nicotine receptor affinity chromatography column. To this end, we have supplied our consultant Professor Leo Abood, University of

Rochester, who is working in close collaboration with us, sufficient quantities of a number of these hydroxynicotinoids. To date, he has had significant success in isolation of a very purified (>500 fold purification) solution of rat brain nicotine CNS receptor(s). A separate report on this work will be issued subsequently. The analogue which has been found to be optimum for this work is 6-(2-hydroxyethyl)nicotine (29). See Scheme XI. The synthesis of additionl hydroxynicotinoids are also illustrated in Scheme XI.

We are also very interested in preparing a nicotinoid which is reactive to nucleophiles; e.g., protein residues. Such a molecule could act by covalently binding at the nicotine receptor(s), thereby contributing to our receptor isolation program. There are other possible utilizations for such a compound, many involving characterization of nicotine's behavioral pharmacology. We have succeeded in converting 6-hydroxymethylnicotine 30 to 6-chloromethylnicotine (31), and we are very optimistic regarding this molecule's future. See eq. 14.

Scheme XI



(a) $(NH_4)_2S_2O_8/H_2SO_4$/methanol

(b) Br_2 followed by Zn/HOAc,

(c) LDA followed by $BrCH_2CO_2$t-Bu,

(d) B_2H_6,

(e) $LiCH_2CH_2OCH(CH_3)OEt$,

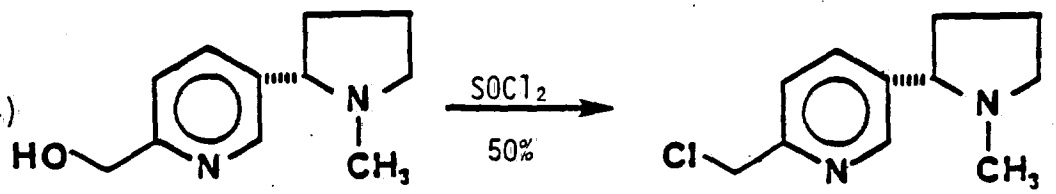
(f) $(NH_4)_2S_2O_8$/t-BuO_2H,

(g) LDA followed by CH_2O,

(h) ethylene oxide,

(i) $NaCNBH_3$

(14)



30 31

$[\alpha]_D^{20}$ -164°

(C 0.4415, CH_2Cl_2)

4. Preparation of Nicotine Analogues

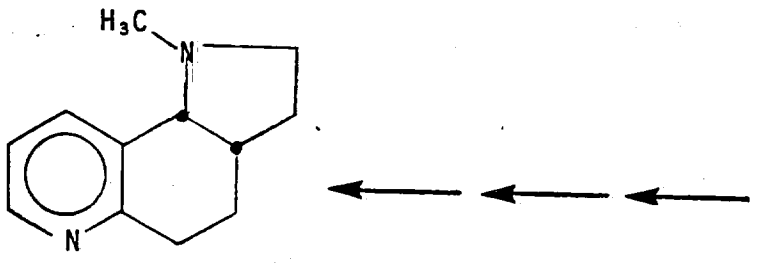
In the previous sections, we have described in detail the preparation of numerous nicotine analogues, of use not only for our pharmacological testing program but also for our nicotine receptor isolation efforts. In this section, we will briefly detail the preparation of a number of additional analogues, usually selected on the basis of previous pharmacological results.

(i) Bridged nicotine analogues are compounds possessing the nicotine ring system but having additional atoms which interconnect two or more portions of the nicotine molecule. The resulting

molecule possesses restricted motion, and often, well-defined conformational properties. These bridged compounds are in general very difficult to prepare, and although there has been considerable interest in their preparation in many laboratories, only one has been reported in the literature to date.

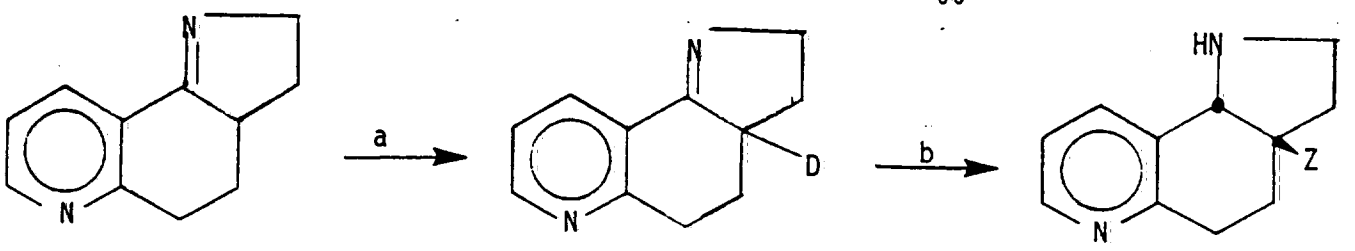
We have previously succeeded in preparing the bridged nicotine, 2,3'-bis-methylene nicotine (32) in a few steps from the quinolone 33 (eq. 15).[5] We have established the stereochemistry of the ring fusion in 32 to be *cis* by the following experiments. The tertiary hydrogen in the bridged myosmine 34 was exchanged for deuterium, as indicated in eq. 16, and was subsequently reduced to the deuterated bridged nornicotine 35d. A comparison of the ^{1}H NMR spectrum of 35d with the ^{1}H NMR spectrum of its hydrogen-substituted analogue 35h allowed us to assign the resonance for that tertiary proton. Jan Wooten then obtained the difference NOE spectrum of 35h at 500 MHz and observed a positive NOE, thereby indicating a *cis* ring fusion for 35h and by inference 32.

15)



32 33

16)

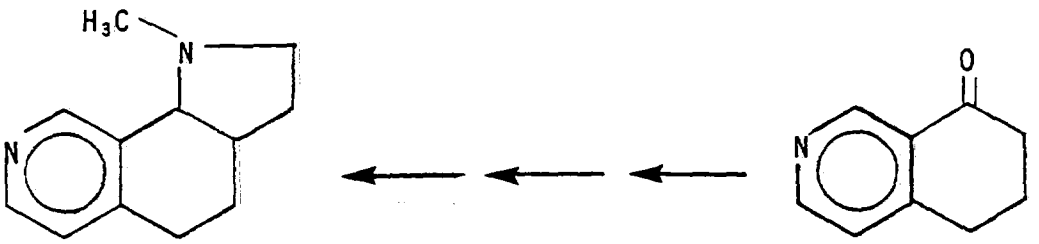


34

(a) CD_3CO_2D, CD_3OD, (b) $NaCNBH_3$.

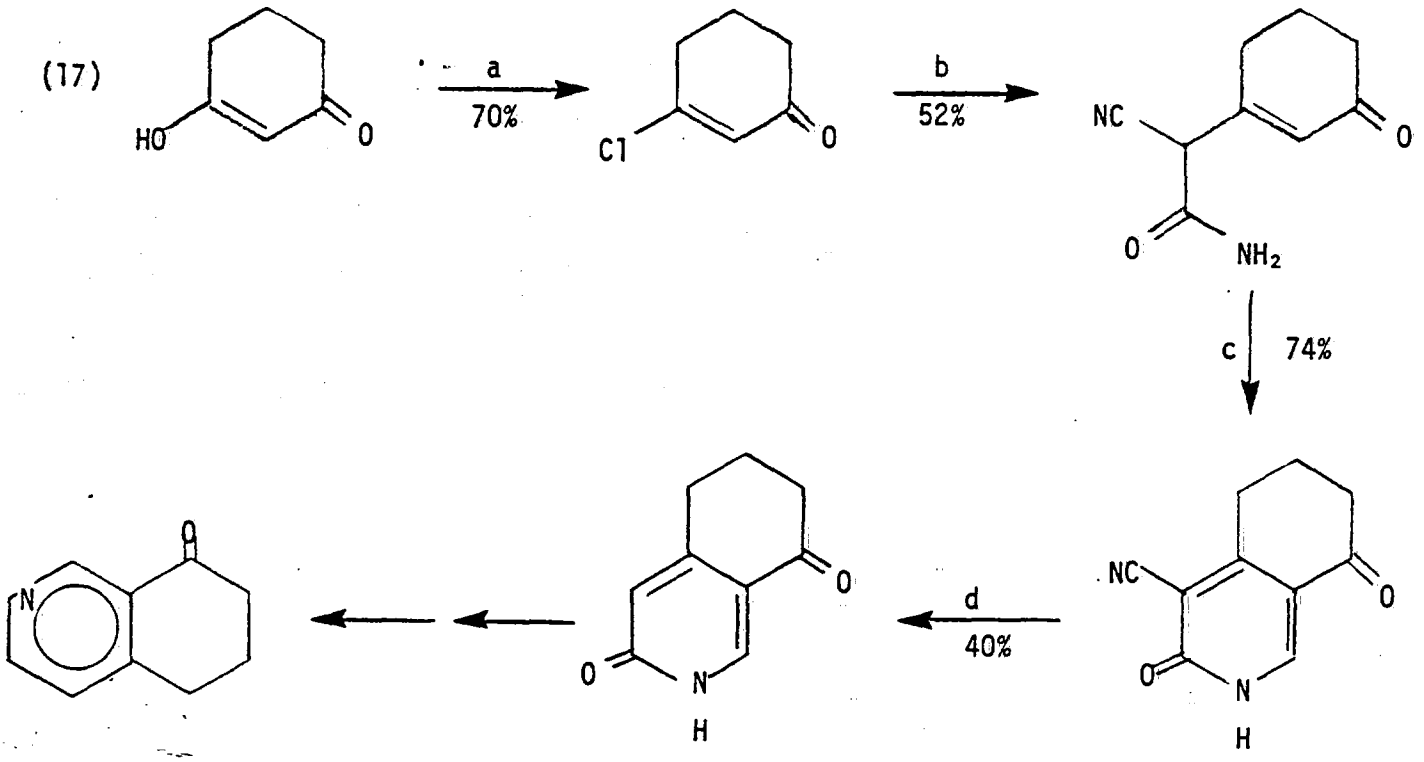
35D, Z=D
35H, Z=H

Having the bridged nicotine 33 in hand, we were desirous of preparing its close analogue, 4,3'-bismethylene nicotine (36). By analogy to our synthesis of 32, we reasoned that the ideal starting material would be 37 (compare eq. 15 with eq. 17). While 32 was readily available, we have found 37 to be less accessible. Equation 17 illustrates the progress we have made to date toward the preparation of 37.[5]



36 37

(17)



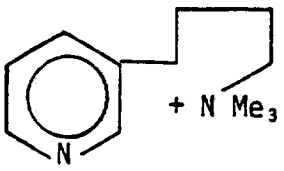
37

(a) oxalyl chloride, (b) $NCCH_2CONH_2$/base, (c) $HC(OEt)_3$/DMF, (d) 48% HBr.

(ii) Table XI lists some of the additional nicotine analogues we have prepared during the last year.[5,6] In some cases, the entries represent compounds previously prepared in our laboratories; additional materials have been required for our testing program. Because of the diversity of these structures and the length of this report, we will not discuss in detail the modes of preparation. Full experimental details can be found in our notebooks and discussions can be found in the monthly reports.

Compounds 38-39 were used to examine the ability of quaternary salts to elicit nicotinic peripheral and central nervous

Table XI. Nicotine Analogues



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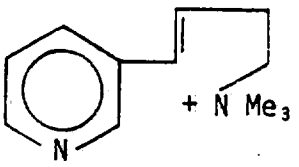

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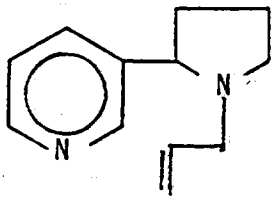

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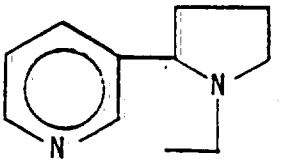

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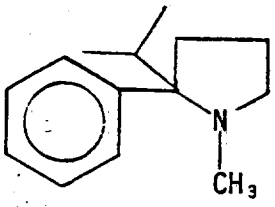

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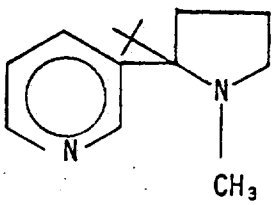

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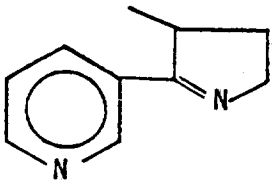

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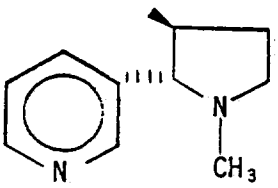

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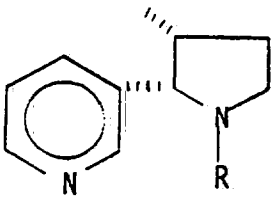
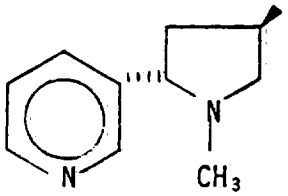


46, R=CH_3

47, R=CD_3



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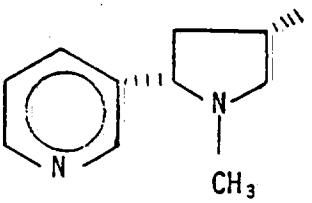

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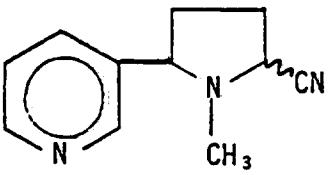

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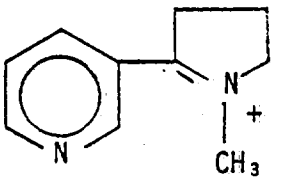

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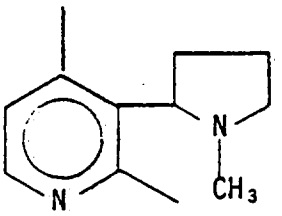

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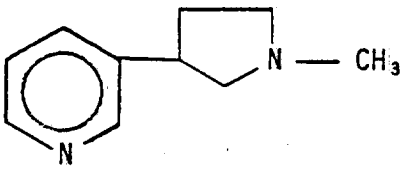

53

system effects; 40-41 are N'-alkyl analogues, the former particularly interesting in that N-allyl opiates have been found to be antagonists; 42-43 are 2'-alkylnicotinoids, of interest due to our finding that 2'-methylnicotine possesses interesting behavioral properties; 44-52 are pyrrolidine substituted analogues, prepared to examine the steric requirements at the receptor(s); 51 is also an important analogue intermediate; and 53 is a ring shifted compound, designed to examine the role nitrogen-nitrogen orientation in the pharmacology.

We have also prepared a variety of nicotine compounds upon request from other groups and these are listed in Table XII.

TABLE XII

Nicotine Compounds Prepared On Request

Nicotine citrate[6]

Anatabine[5]

Four perhydronicotinoids[6]

Two fluorinated nicotinoids[6]

IV. THEORETICAL CALCULATIONS OF TOBACCO FLAVORANTS AND NICOTINE ALKALOIDS[3,4]

In the preceeding sections, we have emphasized the importance of the determination of physical and chemical properties of the flavorants and alkaloids to the goal of generating structure-activity relationships. Over the past five or ten years, there has been an increasing trend in the medically orientated academic community and the pharmaceutical industry to turn their attention to the advantages and implications of theoretical chemistry. In our opinion, theoret-

ical chemistry cannot replace experimental chemistry, nor was it designed to do so. However, theoretical chemistry can make significant contributions to an experimental chemical program, especially one with pharmacological overtones.

For example, theoretical chemistry can calculate the structures and energies of starting materials, products, and in some cases, the transition states connecting the two. It is typically very difficult to determine structural information (bond lengths, bond angles, and dihedral angles); one usually has to resort to x-ray crystallographic analysis, electron diffraction, and microwave spectroscopy. Further, the latter two techniques are useful for very small and usually symmetric molecules. The determination of heat of formation is even less routinely accomplished.

Theoretical chemistry can also be used to model chemical reactions and, in recent years, to model receptor-substrate interactions. Calculations can also be performed to derive other data which are cumbersome to obtain experimentally, e.g., molecular volumes, surface areas, partition coefficients, electron densities, electrostatic potentials, reaction potentials, and more esoteric parameters such as those which index structural similarities and structural complementation.

During the last year, we have begun a theoretical program aimed at assisting both the tobacco flavorant program and the nicotine pharmacology program. All our efforts to date have been in close collaboration with Professors John Schug and Jimmy Viers at Virginia Tech. We noted last year that many of the tobacco flavorants in which we are interested have either a pyridine or a

pyrazine ring -- a structural similarity to nicotine's pyridine ring. We thus put these two classes of compounds together and devised a theoretical program with the following goals:

1. Quantitative description of nicotine and nicotine analogue structure and energetics.
2. Quantitative description of pyridine, pyrazine and pyrrolidine structure and energy.
3. Examine the effect of substitutents on physical and chemical properties of nicotinoids, pyridines, pyrazines and pyrrolidines.
4. Correlation of theoretically derived results with experimental data for the above series of compounds.

To avoid repetition, we recommend that the reader examine Section I of this report. This will provide the background necessary for an appreciation of the basic tenets for this work. The concepts of "chemical reaction modeling of pharmacological activity" and nitrogen accessibility, discussed in the previous sections of this report bear directly on the directions we have chosen in this theoretical approach.

We have utilized complete geometry optimization using the semi empirical all-valence electron MINDO/3 self-consistent field procedures to derive the best structure, for numerous pyridines, pyridinium cations, piperidines, and pyrazines. We have used molecular mechanics to derive structural information regarding a wide series of nicotine analogues. This work has led to the development of a number of models for steric effects in nitrogen heterocyclic chemistry, including pyridines and pyrazines, and has

included the evaluation of substitutent effects on structure and reactivity of pyridines, pyrazines, and piperidines.

Whenever possible, we have validated our calculations with experimental results. For example, we developed a ground state model for the iodomethylation of 2-substituted pyridines, 54, with the orientation of the 2-alkyl group relative to the pyridine ring (NH and θ in 54). The correlation is shown in Figure 11. We have utilized a model transition state (55) to determine the rates of iodomethylation of a very wide range of substituted pyridines, from the reactive 3,4-dimethylpyridine and 4-aminopyridine to the very unreactive 2,6-diisopropylpyridine. This correlation is shown in Figures 12-13. Furthermore, we have correlated the experimental heats of trifluoroborination of twenty five pyridines with our calculated heats of alkylation, thereby substantiating a hypothesis presented twenty years ago by H. C. Brown and his students. This is shown in Figure 14.

The potential implications of these calculations on both our flavor program and nicotine program are pertinent. We are entering the second stage of this work; namely, with the basic foundations derived (structures, bond lengths, angles, etc.), we will now concentrate on the calculation of additional properties of these molecules which will contribute to the structural aspects of our structure-activity relationship studies.

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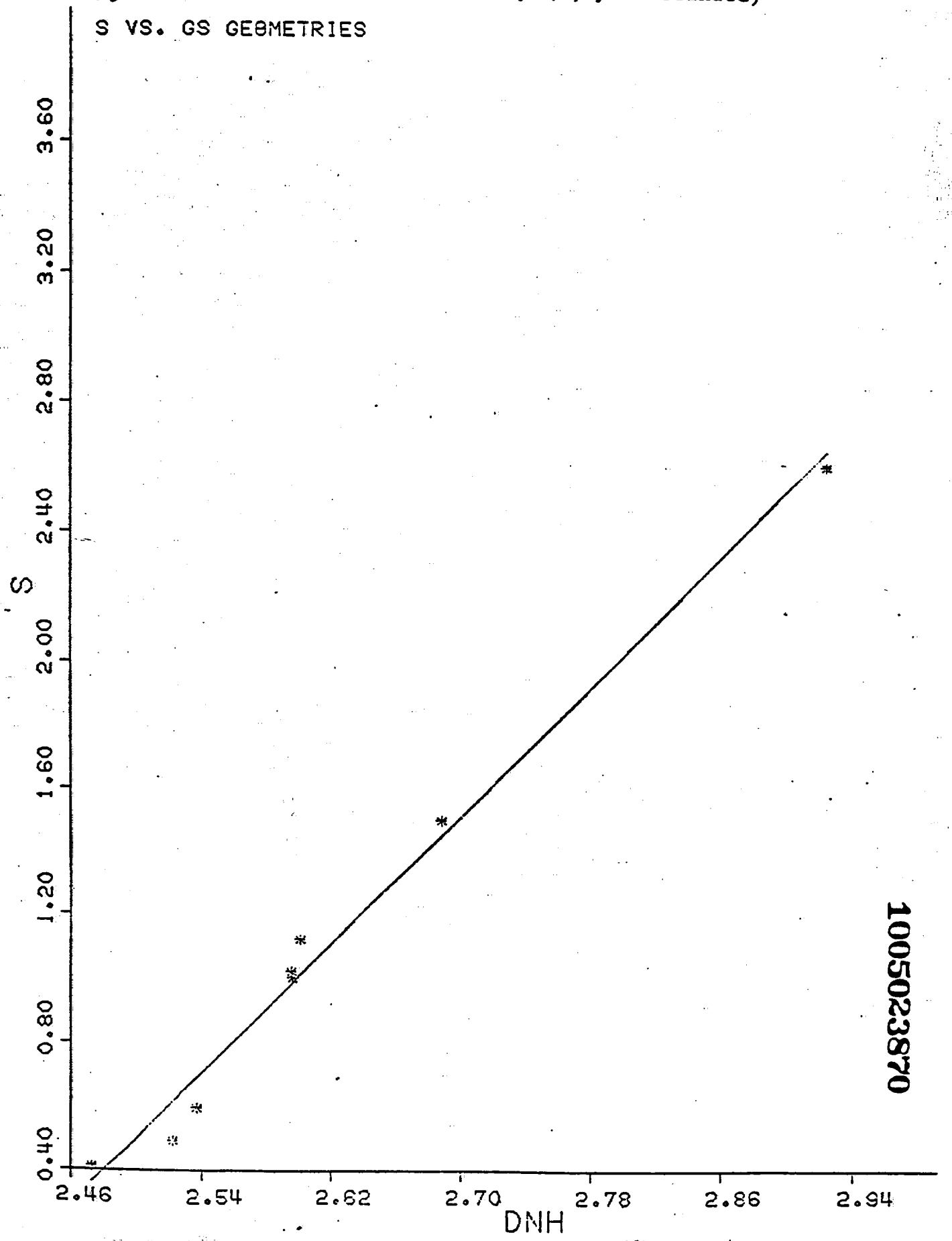
54

Figure 11. Relationship between pyridine ground state geometry (see 54) and iodomethylation reactivity (S, y-coordinate)



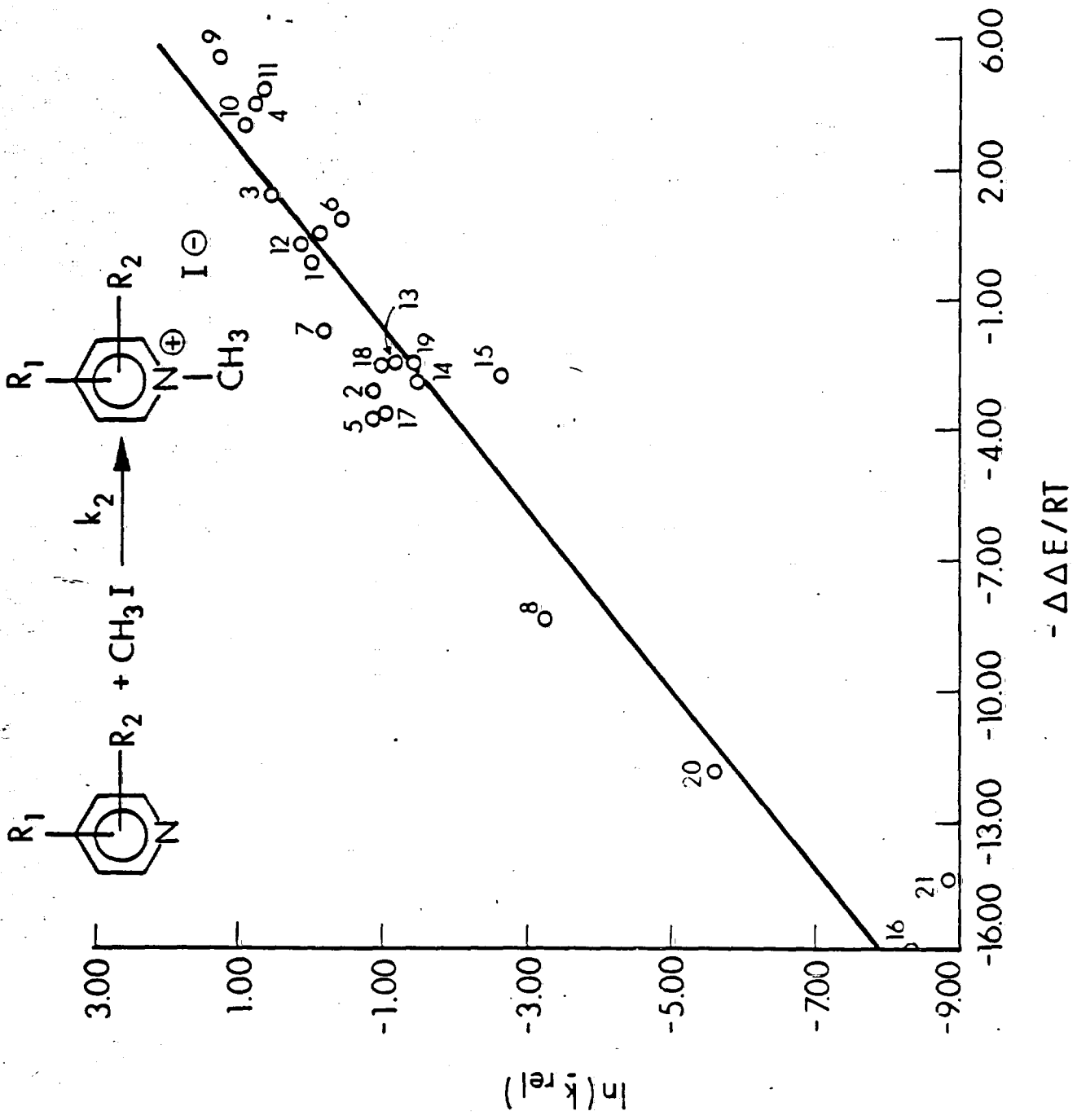


Figure 12. Relationship between MINDO/3-derived activation energy for methylation of alkylpyridines (see 55) and iodomethylation rate constants

Figure 13. Relationship between MINDO/3-derived activation energy for methylation of heterosubstituted pyridines and their iodomethylation rate constants

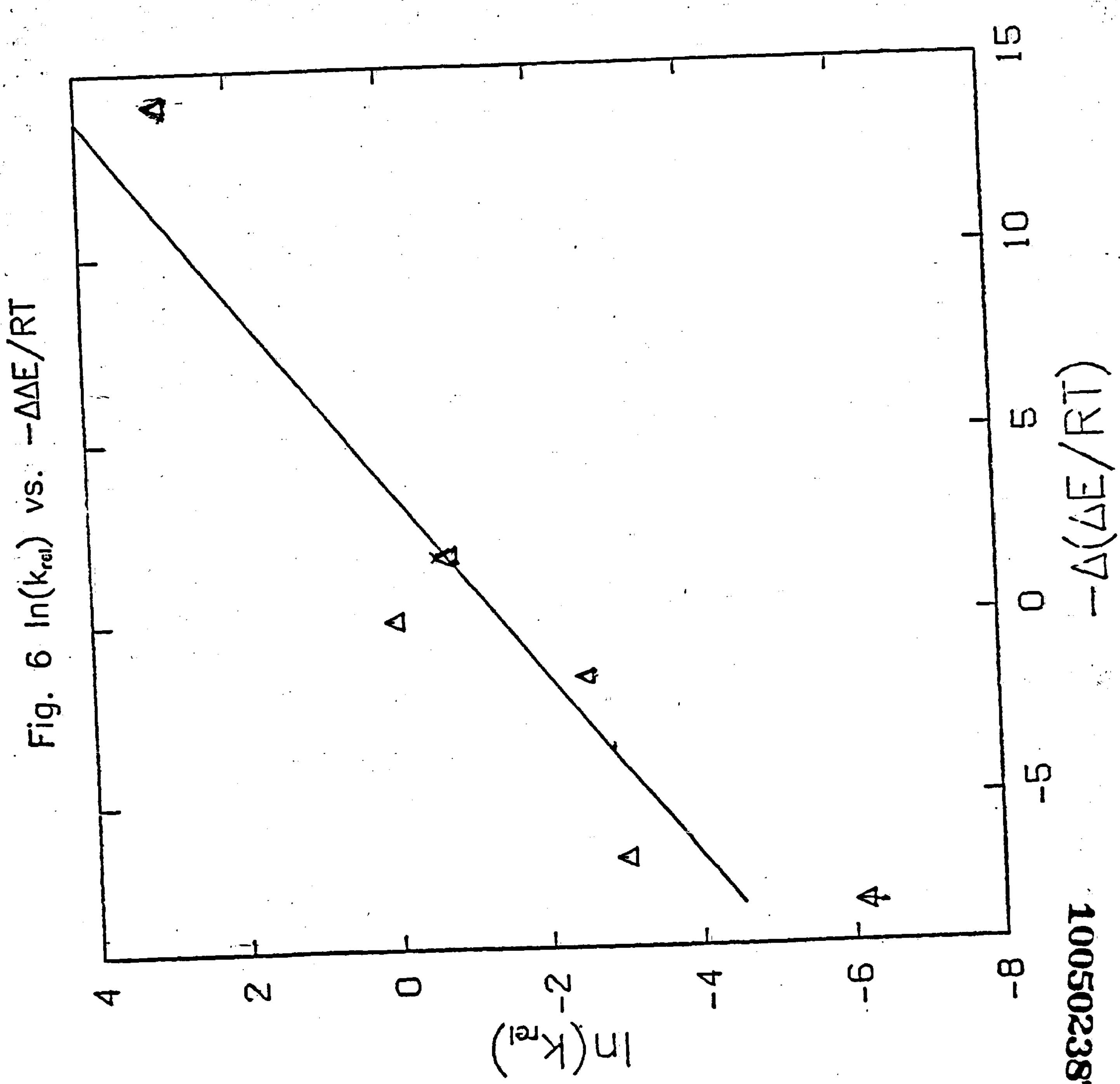
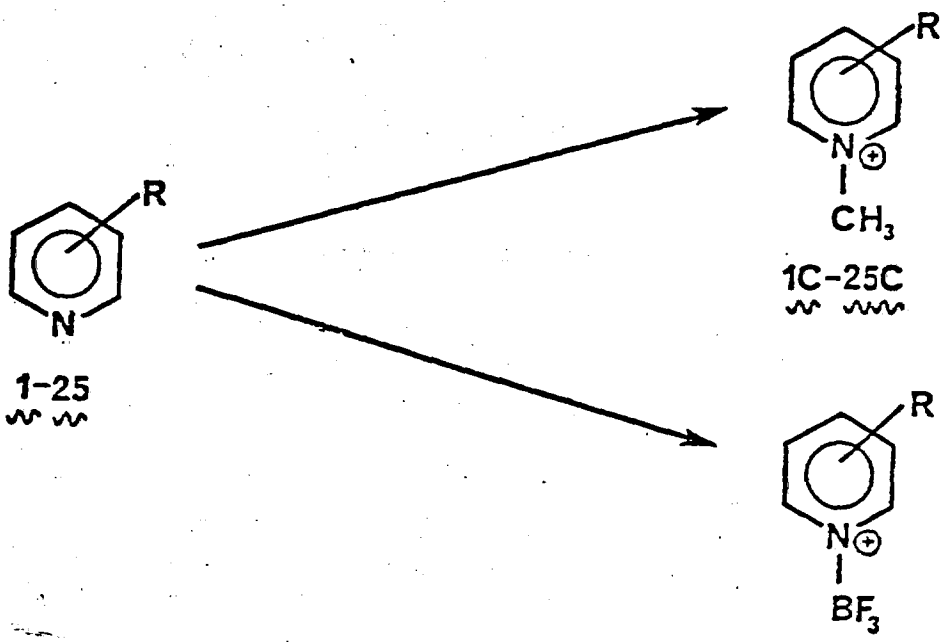
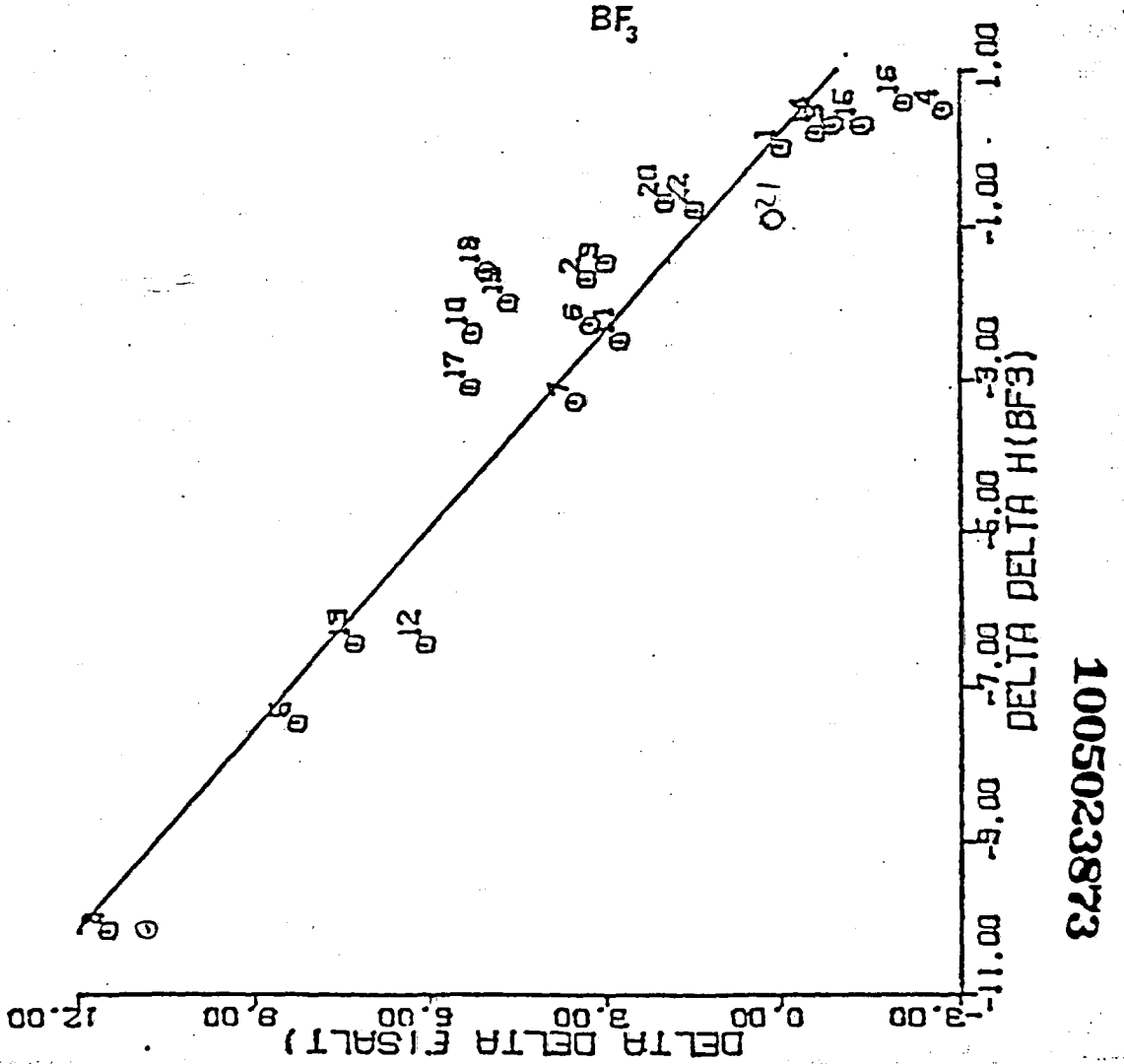


Figure 14. Relationship between MINDO/3-derived energies of methylation and experimental heats of trifluoroboronation for alkylpyridines





Publications

1. C. G. Chavdarian and E. B. Sanders, "Syntheses of (S)-(-)-N-Methylprolinol",Organic Preparation and Procedures, Int., 13, 389 (1981).

2. J. I. Seeman, H. V. Secor, C. G. Chavdarian, E. B. Sanders, R. L. Bassfield, and J. F. Whidby, "Steric and Conformational Effects in Nicotine Chemistry", J. Org. Chem., 46, 3040 (1981).

3. J. I. Seeman, R. Galzerano, K. Curtis, J. C. Schug, and J. W. Viers, "Correlation of Nonadditive Kinetic Effects with MINDO/3 Derived Molecular Geometries", J. Am. Chem. Soc., 103, 5982 (1981).

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7. J. I. Seeman, "The Effect of Conformational Change on Reactivity in Organic Chemistry. Evaluations, Applications, and Extensions of Curtin-Hammett/Winstein-Holness Kinetics",Chem. Rev., accepted for publication.

8. C. G. Chavdarian and J. I. Seeman, "The tert-Butylation of Nicotine: Novel Reaction Pathways and Racemization Studies", Tetrahedron Lett., accepted for publication.

9. C. G. Chavdarian, J. I. Seeman, and J. B. Wooten, "Bridged Nicotines. Synthesis of *cis*-2,3,3a,4,5,9b-Hexahydro-1-Methyl-1H-Pyrrolo[2,3-f]Quinoline", in manuscript review.

10. J. I. Seeman, J. C. Schug, and J. W. Viers, "MINDO/3-Derived Geometries and Energetics of Alkylpyridines and the Related N-Methylpyridinium Cations", in manuscript review.

11. R. H. Cox, H. V. Secor, and J. I. Seeman, "The Conformation of Nicotine: Effect of Electronegative Substituents on the N-Methyl Group", in manuscript review.

12. C. G. Chavdarian, "Optically Active Nicotine Analogues. Synthesis of (S)-(-)-2,5-Dihydro-1-Methyl-2-(3-Pyridyl)Pyrrole ((S)-(-)-3',4'-Dehydronicotine)", in manuscript review.

Patents

1. C. Chavdarian and E. B. Sanders, "Process for the Preparation of Optically Active Nicotine Analogues", U.S. Patent 4,321,387.

2. J. Seeman, "Smoking Compositions", U.S. Patent 4,312,367.

3. E. Southwick, D. Williams, and Y. Houminer, "Production of Monoacylpyrazines", U.S. Serial #307,262.

4. J. Seeman and E. B. Sanders, "5-Alkyl Nicotines and a Process for their Production", U.S. Serial #132,557.

V. ACKNOWLEDGMENTS

In addition to those individuals and groups whom we have cited as making major contributions to this work in Section I, we are pleased to acknowledge the assistance and cooperation of members of the Chemical Research Division, the Flavor Development Division, the Computer Applications Division, and the Analytical Research Division. We especially acknowlege Drs. T. S. Osdene and E. B. Sanders for their continuous input and encouragement. This report was written with the splendid cooperation of all members of the project, with the particular contribution of R. Southwick who authored portions of the Flavor Chemistry section. This report was typed by Anne Donathan and most of the drawings were done by Melanie Allgood, both of whom we render sincere thanks.

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